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Quantitative and objective assessment of motor functions in subjects affected by Parkinson's disease by using a 3-axial accelerometer sensor and machine learning techniques.

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Abstract

This thesis presents the results achieved using 3-axial accelerometer data to objectively assess the motor functions in patients with Parkinson's disease (PD). Clustering and classification techniques are used to research a relationship between the motor assessments, given by the machine learning algorithms, and the clinical scores, derived by neurologists' evaluations while patients performed several standardized motor tasks.
The accelerometer signals are pre-processed and analyzed to extract features able to assess the severity of the PD patients motor symptoms. K-Means and Expectation-Maximization algorithms are applied on the dataset to research and to define primary grouping rules among the different subjects. The clustering evaluations are carried out, firstly, to detect an inter- variability of the movements while the patients were performing a specific motor task. Moreover, the clustering techniques are also used to group several patients in the same cluster, testing their similarity in terms of clinical rating scores. The clustering results are, finally, validated by using Bayesian Classifiers. In particular, the Naive Bayes classifier is employed to verify the reliability and the stability of the assessed grouping rules defined in the clustering problems.
From a more forward-looking perspective, the entire analysis has been done to use the validated motor detection technique for the research of the relationships between the patient's sleep patterns and PD motor symptoms.

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Abbreviations

A-DOPA	[assessment] before the last **DOPA**minergic **A**fternoon drug intake, before dinner
BRAIN (test)	**BR**adykinesia **A**kinesia **A**kinesia**IN**co-ordination **(test)**
CMS	**C**ardinal **M**otor **S**ymptoms
E	**E**vening at bedtime
M-30	[assessment] **30** minutes after **M**orning awakening
M-DOPA+1	[assessment] **M**orning **1** hour after the first **DOPA**minergic drug intake
MDS-UPDRS	[assessment] **M**ovement **D**isorders **S**ociety **P**arkinsons **D**isease **U**nified **R**ating **S**cale
PD	**P**arkinsons **D**isease
RBD	**R**EM **B**ehaviour **D**isorder
REM (sleep)	**R**apid **E**ye **M**ovement **(sleep)**
SB	**S**leep **B**enefit

To my mother and my father ...

Chapter 1

Introduction

1.1 General Context of application

So far, the research on the relationships between sleep and PD focused on the impact of Parkinson's disease (PD) symptoms or PD-associated neurodegeneration on sleep. Motor function and sleep are in fact intrinsically intertwined in PD [11]. Sixty-five to 95% of PD patients report disturbed sleep or daytime sleepiness [12, 13], which further impair their quality of life or of their families [14, 15]. Indeed, nocturnal motor symptoms of PD are taught to disrupt nocturnal sleep in these patients [16]. On the other hand, the relationship between sleep and motor function in PD has been more recently explored from a different standpoint, i.e. looking at sleep-related phenomena to better understand how motor function is regulated in PD [17].

During the sleep-related disorders, mainly observed during stable Rapid-Eye-Movements (REM) sleep phase in PD patients with REM behaviour disorder (RBD), the complex behaviours seem to be more fluent and vigorous than the voluntary movements performed by the same patients during wakefulness [18]. The same complex behaviours can be observed also upon arousals from REM sleep (pseudo-RBD) [19]. Thus, during RBD and pseudo-RBD sleep-phenomena may be interesting to explore and to objectively characterize the motor functions in PD patients.

Even more interesting is the proof of evidence of the so-called Sleep Benefit (SB) phenomenon. A substantial proportion of patients with PD report prominent spontaneous, transitory improvements in motor function after nighttime sleep and before taking the first morning dose of dopaminergic medications.
A recent definition of SB was proposed by van Glist et al. [20]: *"the experience of a temporary decrease in PD symptoms upon awakening after a period of sleep (night or*

daytime), before drug intake; the patient is feeling as good as "on" or even better".
In previous researches are reported percentages ranging from approximately 30 to 55% of PD patients (and up to 72% of them according to a recent questionnaire-based study [21]) experiencing SB phenomenon [20, 22–27]. A better understanding of the underlying mechanisms of SB could pave the way to new therapeutic strategies addressing motor disability in PD patients.

Therefore, an improvement in motility in PD is observed during REM sleep in PD patients mainly with REM sleep behaviour disorder. As REM sleep is mostly concentrated in the final part of the nocturnal sleep period, one can speculate that SB might be explained by a morning carry-over effect of REM sleep after wake-up time.

1.2 Aim and Outline of the study

As during RBD and pseudo-RBD, the sleep periods preceding the SB might be of particular interest to objectively analyze the motor function of the subjects and, particularly, to understand the nature of this inconstant SB phenomenon.
In this scenario, the primary need to develop an algorithm able to define and to detect the main characteristics of the abnormal movements in PD occurs. Thus, in the following study, the ultimate goal would be to design an instrument based on an objective pattern recognition and so an objective measure of PD patients motor functions.

By using wrist-wearable accelerometer sensors, characteristic motor features are extracted from the raw data while the subjects are performing a specif upper-limb motor task. The data will be analyzed on the hypothesis that the patients should be under the same condition - levodopa daily drug.
The data need to be previously pre-processed, according to the cardinal motor symptoms wishing to detect. Then, feature extraction procedures have been carried out on the wake of several previous studies by Noel L.W. Keijsers et al. and Shyamal Patel et al.. These latter shared the common goal of monitoring PD motor fluctuations and predicting the severity of their motor symptoms [28, 29]. The methods and the characterizing parameters used in these studies have been considered to be appropriate and broadly applicable to our case of study. This is because the designed data attributes were strictly linked to the specific cardinal motor symptoms needed to be identified.
In the study statistical clustering approaches, k-Means and Expectation-Maximization algorithms, are applied on the extracted dataset to estimate a primary inter- variability detection of the PD patients motor functions.

Moreover, the research of a relationship between the estimates of the grouping algorithms and the clinical rating scores is carried on. The outcomes of the grouping algorithms, obtained for each subject, shall comply with the clinical Unified Parkinson's Disease Rating Scale (UPDRS) score given by the neurologists. In this way our instrument may be considered as an applicable and validated future tool able to score the severity of the Parkinson's upper limb motor skills.

Finally, further classification techniques are used as validation tools to verify the grouping rules defined by the clustering approaches. In particular, probabilistic based algorithms, Bayesian classifiers, are tested on the dataset to compare the estimates with the previous clustering results.

Chapter 2

Parkinson's Disease Pathophysiology

Idiopathic Parkinson's disease (PD) is a neurodegenerative movement disorder affecting 1.5% of subjects older than 60 years [30]. Its prevalence in general population is estimated between 1/10000 and 4/1000 [31]. A progressively impaired motor function leads to loss of autonomy in daily living and reduced quality of life of PD patients [32]. Voluntary movements in PD patients are slower (bradykinesia), of reduced amplitude (hypokinesia) and less fluent than in healthy subjects. Moreover, resting and action tremor, rigidity, impaired equilibrium and gait further interfere with patients' daily living [33].

" Involuntary tremolous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forewards, and to pass from a walking to a running pace: the senses and intellect being uninjured " [34].

Above the classical, but still current, clinical description of six cases of study palsied patients condition, given by James Parkinson. The original description precludes any kind of cognitive impairment, affirming the absence of mental state alterations. This latter theory, instead, was formulated by Trousseau and Charcot in the half of last century only [35].

"Shaking palsy" represents the most frequent and well-defined form of motion disorder caused by the degeneration of dopaminergic neurons of a small brain's area called

substantia nigra (SN). Physiologically, PD motor symptoms are due to basal ganglia network dysfunction. The fronto-basal network is a cortico-subcortical motor circuit contributing to voluntary and automatic movements by "smoothing" the motor programs elaborated by the motor cortex [36]. PD-related neurodegeneration leads to cellular loss of dopaminergic neurons of the brainstem's substantia nigra, which in turn is involved in the correct functioning of the basal ganglia circuit [33].

The treatment of PD motor symptoms is currently purely symptomatic and relies on pharmacotherapy (e.g. levodopa drug), which enhances dopaminergic neurotransmission in the brain [37]. However, this approach often fails to optimally improve motor abilities of the patients in the middle- and long-term and is associated with side effects that limit its use, especially in the advanced stage of the disease [37]. An alternative therapeutic approach to improve motor symptoms is the modulation of basal ganglia activity by electrical stimulation of one of the hubs of this circuit (more frequently the subthalamic nucleus) by mean of electrical currents delivered by intracerebral electrodes, the so-called deep brain stimulation. However, this technique only applies to very selected patients with advanced PD stage [38, 39]. Thus, the development of innovative non-invasive therapeutic strategies for PD motor symptoms is not only a research challenge, but also a clinical demand. In this context, sleep research might bring promising insights into PD therapeutics for motor function.

2.1 Disease Evolution

Parkinson's disease is mainly characterized by two phases: pre-symptomatic and symptomatic. In the first pre-symptomatic phase the dopaminergic neurons decrease, although, it is not yet clear when this stage begins, nor what is the percentage loss of the dopa neurons. Basing on several research studies some theories have been formulated, such as the one stating that it would spend five years between the beginning of the dopaminergic neurons reduction and the first symptoms appearance[40]. Another current of thought asserts that the loss of neurons can begin even about forty years before the onset of the disease. Unfortunately, as regard the patients, it is very hard to detect the precise moment in which the first symptoms occur.
However, it is possible to classify the symptomatic phase of PD in the early phase and the late phase. The first one is characterized by the appearance of the first PD symptoms, arising when approximately 70% of the dopaminergic neurons of the substantia nigra are lost. The second phase refers to the time span of the pathology progression.

The primary motor symptoms may occur with a certain variability; some patients may have all cardinal motor symptoms, others may show, only, tremor or akinesia and rigidity. A characterizing feature of Parkinson's disease is the high number of symptoms, both motors and non-motors. All these symptoms lead to heavy repercussions on the quality of life of the subjects. In many studies it has been observed that the neurodegeneration of the nigrostriatal dopaminergic neurons is preceded by extracellular neuropathological variations. As a result, the motor symptoms may appear also 10 years after non-motor ones.

According to the Hoehn and Yahr scale [41] it is possible to classify Parkinson's disease in 5 different stages:

Stage I - the patient shows an unilateral mild resting tremor disorder to the upper limbs, slight rigidity, presence of akinesia and the rapid alternating movements impairment. It is remarkable the slowdown and the worsening of the periodic movements (e.g. writing troubles, micrographia). In addition, facial hypomimia and frontal seborrhoeic dermatitis are stored.

Stage II - mild bilateral involvement with early postural alterations. The subject assumes a fixed posture where trunk, hips, knees and ankles are slightly slumped. Moreover, all movements tend to slow down gradually, causing the so-called bradykinesia phenomena. Patients often experience a reactive depression.

Stage III - mild to moderate bilateral disease, general disability, abnormal gait and appearance of a retropulsion/propulsion. An increasingly hasty and short step is remarkable, with the trunk tilting forward. There is an important slowdown in gait and an increase in bradykinesia disorder. The patients in this stage may need external help to perform some tasks.

Stage IV - severe disability, able to walk or stand unassisted. The subject need more assistance in carrying out normal daily activities and is no longer able to live alone. At this stage the patient has frequent fall, and tasks requiring fine motor skills become difficult or impossible.

Stage V - complete disability (wheelchair bound), the patient is bedridden unless aided. An immobile supine position is assumed.

2.2 Motor Symptoms

The cardinal motor symptoms (CMS) are abnormal movements such as rhythmical limb shaking of specific frequency and amplitude (resting tremor), increased involuntary muscle tension (stiffness or rigidity), slowness in the execution of movements (bradykinesia), inability to initiate voluntary movements (akinesia), postural instability and also sleep-related abnormal movements (e.g. night parkinsonian dystonia/cramps, periodic limb movements, abnormal chest movements during respiratory events, movements during dream enacting). These motor symptoms, in most cases, appear asymmetrically, that is one side of the body is more affected than the other.

2.2.1 Resting Tremor and Bradykinesia

The majority of Parkinson's patients exhibit the resting tremor symptom. It may be considered as the symptom of the onset of the disease, even though, often, it does not show a remarkable evolution over the years.
Rest tremor can be defined as a rhythmic oscillatory involuntary movement, occurring when the affected body part is not voluntary activated and is completely supported against gravity [42–44]. In Parkinson's disease, resting tremor frequency is in a range of 3-6 Hz, and it is characterized by an amplitude of the movement from 1 to over 10 cm wide [1]. Tremor phenomena may affect an hand as also feet, jaw and tongue as well.
In literature two theories have been developed to try to explain the pathophysiology of the resting tremor symptom. The first one is based on the presence of some cells that are rhythmically active before tremor. These cells may represent a tremor "pacemaker" located in the intermediate ventral nucleus [45]. Consequently, the pyramidal fascicles transmit the thalamic rhythmic activity to spinal motor neurons.
In the second theory, however, it has been shown that the resting tremor can be generated by voluntary movements. In that case, a neuronal circuit including muscle spindles, thalamus, motor cortex and ending through pyramidal fascicles on motor neurons, may also cover the tremor "pacemaker".

Other forms of tremor in PD are the action tremor subdivided into postural tremor, intention and kinetic tremor. The first one comes about when the patients voluntarily maintain a position against gravity (e.g. stretching out the arms). The intention and kinetic tremors, instead, are present respectively during target-directed movements and voluntary movements. Another type of tremor, reported frequently even in the initial stage of the disease, is the internal tremor. It is a not visible internal vibration, producing a quivering sensation inside the arms, legs, chest or abdomen of the patients.

The bradykinesia is a slowdown in the performance of movements with a progressive loss of speed and amplitude during specific rapid movements. Physiologically, the premotor area of the cerebral cortex should be able to ensure the movements execution when the motor behaviour is still not well defined. However, in case of damage to the ganglia, the less flexible and less accurate cortical mechanisms replace them. The result is a loss of automaticity in patient's movements. The bradykinesia can be assessed by asking the patients to do fine manual repetitive movements (e.g. tapping thumb and index fingers), in order to detect a possible progressive slowness and loss of amplitude.
However, there are other evident common symptoms related to the bradykinesia disease including the modification of the handwriting (micrographia), the sialorrhoea (increased amount of saliva in the mouth) due to a slowing down of the muscles involved in swallowing, the hypomimia (reduced facial expressions), the shuffling, the freezing muscles and so on. The bradykinesia symptom causes also a loss of the patients ability to speak clearly. The voice becomes softer over the time (hypophonia).

2.2.2 Rigidity and Postural & Gait Impairment

The rigidity may be the first symptom of Parkinson's disease. The stiffness is an involuntary increase of the muscle tone. It can cause inflexibility of the muscles, pain and muscle cramps. Often, it begins on one side of the body, but many patients do not notice it as they report only a bad feeling of discomfort. The pathophysiology of the stiffness symptom is not yet known. A reliable hypothesis asserts that there is an excessive over spinal activity, turning into an inability of the patient to relax the muscle mass.

The instability or loss of balance is another recurring symptom in PD, and it occurs in the course of an advanced disease. The symptom involves the body axes, and it is due to a progressive reduction of righting or postural reflex [46–48]. The subject is no longer able to spontaneously correct any imbalances tending to adopt a stopped posture.
The instability occurs mainly when the patient is walking or changing direction along the way, and it might cause a greater chance to fall. Therefore, the gait become slow, simple movements as turning around are performed with multiple little slow steps. Clinically, the pull test is used to analyze the postural stability disorder. It consist in applying a pull to the patient's shoulders to check the suddenness of the postural response of the subject.

2.3 Non-motor Symptoms

Parkinson's disease is usually regarded as a motor disorder, even though patients with PD record several critical non-motor symptoms (Table in figure 2.1). Among the main non-motor symptoms autonomic dysfunctions (alteration or distortion of the perception of smell, urinary dysfunction), gastrointestinal diseases, neuropsychiatric disorders (depression, sleep disorders) and sensory disorders occur. The depression as well may be considered as the most common symptom in PD cases. Generally, it precedes any kind of motor symptom or occurs within one year of the onset of the disease.
In recent studies several non-motor symptoms have been analyzed for diagnostic purposes but also to improve the quality of life of the patients [4, 6, 8]. Since PD is a progressive pathological disease, are been identified cases where some of these non-motor characters such as REM behaviour disorder, constipation, hyposomia and depression shall be used as potential diagnostic items in earlier disease phases [7, 49–51].

Neuropsychiatric features
Apathy
Anxiety, panic attacks
Mood disorders, especially depression
Hallucinations, illusions, delusions
Cognitive deterioration, ranging from mild impairment to dementia
Dysautonomia
Orthostatic hypotension
Constipation
Urinary dysfunction (urgency, retention)
Sexual dysfunction
Excessive sweating
Seborrhea
Sialorrhea (i.e., drooling, also attributable to decreased swallowing movements)
Sleep disorders
Insomnia
REM behavior disorder
Restless legs syndrome
Periodic limb movements in sleep
Excessive daytime sleepiness
Sensory dysfunction
Hyposmia (i.e., loss of sense of smell)
Decreased visual contrast and color discrimination
Decreased visual motion perception
Abnormal sensations, such as paresthesias (i.e., tingling)
Pain
Fatigue

Data from Silva et al. 2005; Emre et al. 2007; Poewe 2008; Castelo-Branco et al. 2009; Chaudhuri and Schapira 2009; Lim et al. 2009; and Gallagher et al. 2010.
Abbreviation: REM, rapid eye movement.

FIGURE 2.1: Background list of non-motor symptoms stored in PD affected subjects [1–8].

Chapter 3

Materials and Methods

The whole study is made on the wake of a recent research project conducted in the Neurocenter of Southern Switzerland, Regional Civic Hospital of Lugano, by Dr. Pietro-Luca Ratti. The project is in cooperation with the Department of Innovative Technologies (DTI), at the university of SUPSI, Manno Switzerland.
The study title is *"Sleep, Awake & Move. Systematic characterization of sleep benefit in Parkinson's disease and role of nocturnal sleep and REM sleep at morning awakening. An observational, prospective study and an interventional cross-over study"*. The study aims at systematically characterizing Sleep Benefit (SB) and the day-to-day variation of this phenomenon in patients with PD (Sleep & Move); furthermore it aims at testing the hypothesis that objective and/or subjective improvement of motor function might be due to a carry-over effect of REM sleep at awakening from this sleep phase, in a subgroup of consecutive, unselected PD subjects (Awake & Move).

The *"Sleep, Awake & Move"* project is mainly structured into three visits :

- The first baseline visit (V0) is taken immediately after the signature of the informed consent. In this primary visit the eligibility criteria is validated. The subjects are examined and subjective questionnaires and scale are administered asked to keep their habitual medications, sleep and wake routines unchanged during the all duration of the project.
  At V0, Sleep & Move visit, each participant is instructed on the procedures she/he is asked to run independently at home during 2 weeks (from the evening of day 0 to the morning of day 14, Sleep & Move home monitoring). Subjects are asked to run, in their home environment, objective and subjective, prospective and retrospective self-administered BRAIN (BRadykinesia Akinesia INco-ordination) tests four times a day. The tests are based on an alternating finger tapping movement performed on a keyboard. The subjects have to alternatively strike two target keys as

fast as possible for 30 seconds. These motor tasks are performed 30 minutes after morning awakening (M-30), in the morning one hour after the first dopaminergic drug intake (M-DOPA+1), in the afternoon just before the last dopaminergic drug intake, before dinner (A-DOPA) and at bedtime in the evening (E). Each subject has the possibility to perform an extra assessment per day in the case he would subjectively perceive sleep benefit (for instance, after a nap).

A 2-week continuous actigraphic recording is carried out to characterize the sleep and wake patterns. Wrist actigraphy is donned at V0 and offed at V1. Actigraphic measures are performed according to standard routine clinical practice.

At V0, a study diary and a tablet computer with an external keyboard adapted for the BRAIN test is also given to each subject, which is asked to return them at the end of Sleep & Move study visit (V1).

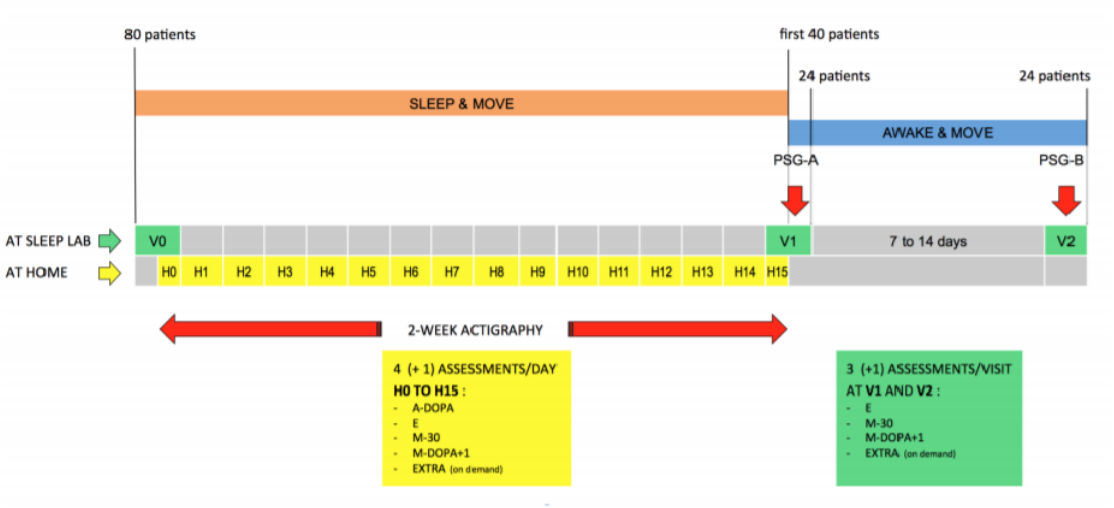

FIGURE 3.1: Flow chart of project assessments.

- At V1 and V2, Awake & Move first and second visit, subjects are asked to run the same subjective and objective prospective and retrospective self-administered tests of the Sleep & Move study (part I of the project) in three moments: at bedtime (E), 30 minutes after morning awakening (M-30) and one hour after the first dopaminergic morning drug intake (M-DOPA+1), in the same way as in the Sleep & Move study. The MDS-UPDRS-III (Movement Disorders Society Unified Parkinson's Disease Rating Scale; part III, motor examination) is also administered in V1 and V2 at the same times of the other assessments (E, M-30 and M-DOPA+1).

  The MDS-UPDRS scale is a revision of the original UPDRS scale [52], the most widely used clinical rating scale for PD. The MDS-UPDRS scale rates 65 items, regrouped across four parts: part I ("non-motor experiences of daily living), part

II ("motor experience of daily living), part III ("motor examination) and part IV ("motor complications), based on two self-based questionnaires (part I and II), clinical examination (part III) and an examiner-conducted clinical interview (part IV). The participation of each subject to the study terminate at V2 visit.

In the figure below 3.2 is tabled a brief summary regarding procedures and some other assessments of the *"Sleep, Awake & Move"* project, tightly tied up with our study.

	BASELINE	Part I SLEEP & MOVE			Part II AWAKE & MOVE		
Study Periods	**SCR**	**V0**		**H0 to H15 at home, repeatedly**	**V1**		**V2**
Patient Information	x	x					
Eligibility criteria		x					
Informed Consent		x					
Demographics		x					
Medical History + CIRS-G		x					
Neurological examination, MMSE		x					
MDS-UPDRS		x			x	x	x
PSQI		x			x	x	x
PDSS-2		x			x	x	x
ESS		x			x	x	x
FSS		x			x	x	x
SB questionnaire		x					
BDI		x					
Home self-assessed procedures explanation & verification			x				
Training to BRAIN test			x				
Actigraphy				2 weeks continuously			
BRAIN test (at V1, V2: also MDS-UPDRS-III)				x 4 [+1] times/day: - A-DOPA - E - M-30 - M-DOPA+1 - [on demand]		x 3 [+1] times: - E - M-30 - M-DOPA+1 - [on demand]	x 3 [+1] times: - E - M-30 - M-DOPA+1 - [on demand]
VAS							
SSS							
SCOPA-DC							
Sleep diary				x once/day			
Exclusion of subjects with undistinguishable NREM/REM sleep patterns or sleep disordered breathing						x	
REMSA						x *	
NREMSA							x *
Night diary						x	x

* REMSA or NREMSA. SCR= screening visit

FIGURE 3.2: Summary of the project procedures and assessments.

3.1 Raw Data Collection

Twenty-one male and female subjects are recruited in our study (from patient number SAM021 to patient number SAM041 of the total 80 patients of the *"Sleep, Awake & Move"* project), ranging from 43 to 86 years old. Basing on the Hoehn & Yahr motor score, the eligibility criteria is made considering patients with mild to moderate-severe stage, namely in Hoehn-Yahr stage II to III. The reason is that in a very mild forms of the disease, slight fluctuations of motor functions might not be detectable neither on a subjective basis nor at objective testing. On the other hand, patients with very severe forms of PD might be too impaired to be able to perform the study assessment in a home setting.
In addition all the patients are always considered in an "on" state, that means "on" medication effect. Habitual hypnotic medications or other habitual psychotropic agents are allowed during the subjects' participation to the project, provided that they are kept at the same dose and times of administration. No treatment modification are allowed.

In the study, the data analyzed are related to the output of the wrist 2-week continuous actigraphic recording, and to the output of the actigraph in V1 and V2 visits. In both cases, the data are taken into account when the subjects are performing the BRAIN motor task tests as described above.
Thanks to the *"Sleep, Awake & Move"* project, in the Sleep & Move study is set up a tablet application including subjective assessments of sleep and motor function: bringing at patients' home a validated test to objectively assess motor function in patients with Parkinson's Disease (the BRAIN test), in co-operation with Dr. Eun Kyoung Choe of Pennsylvania State University, PA, U.S.A. and Dr. Alastair Noyce from the University College of London, U.K.. These instruments may be employed in the short term also for better monitoring patients' symptoms and signs in routine clinical practice and also for future research.

3.1.1 BRadykinesia Akinesia INco-ordination (BRAIN) test

The BRAIN test is a software test that is based on an alternating finger tapping test, which measures neurological signs of PD by evaluating upper limb motor function (see figure 3.3). It uses a standard personal computer with the keyboard as the test device. The two targets are the "A" and ";" keys which are 15 cm apart on the 101/102 keyboard. The target keys are marked with adhesive red paper dots 10 mm in diameter. The participants to this project are provided of a tablet computer with an external keyboard and are instructed to seat comfortably in front of the keyboard at a height that allows their arms to be above the keyboard when their elbows are flexed at 90°. Using the

index finger, the subjects have to alternatively strike the target keys as fast as possible during a period of 30 seconds. Before starting the test the subjects are told to perform the test as fast and as accurately as possible [53].
Note that the motor task described above has the same characteristics of the movement of the finger-to-nose test (standardized motor task), reaching and touching a mark.

The main advantage of the BRAIN test is that it has been validated as a sensitive software tool for detecting neurological signs of PD [53]. In addition, it is a very easy-to perform motor task, it is a very rapid-to-administer test (less than 5 minutes on both upper limbs), it suitable to be employed in a home setting, as it can be self-administered by PD subjects without an examiner, it is based on a software program that is not influenced by the examiner's individual assessment bias and it can be employed free-of-charge with a standard laptop computer or tablet.

FIGURE 3.3: Tablet guideline of the BRAIN test performed using the left index [top] and the right index [bottom].

3.1.2 Wrist Actigraph

An actigraph is a small wristwatch-type wearable device that monitors and records upper limbs movements over time by using a tri-axial accelerometer. Raw data are recorded employing multichannel actigraphs which combine the measures of movement, light exposure and near-body temperature (GENEActivTM, Activinsight Ltd., Kimbolton, Cambridgeshire, UK, figure 3.4).
A tri-axial accelerometer is composed by three mutually orthogonal uni-axial accelerometers, where each axis (X- Y- and Z-) measures the sum of the gravitational -mass of the earth- and the inertial -applied to the device- acceleration components. The acceleration $\vec{a}$ of a body can be seen as its rate of change of velocity and it is directly proportional to all external forces $\vec{F}$ acting on the body. Hence, an accelerometer measures accelerations due to all forces acting on the device.

FIGURE 3.4: GENEActive raw data wrist-Actigraph [left]. Device axis-arrangement X- Y- Z- [right] [9].

The sensor used in our study works in a range of $\pm 8g$ (g $= 9.8 m/s^2$) with a resolution of 12bit ($3.9mg$), and it offers a recording sample rate capacity at up to 100 Hz. The sensor should be fitted to the patient's wrist with the serial number in the correct orientation showed in figure 3.5.
The actigraphy offers several advantages that make it suitable for our study: it is relatively inexpensive and therefore particularly apt for studies over an extended period of time; it is a non-invasive method for long-term monitoring of the human rest/activity cycles; in addition, the actigraphs are used at home during routine daily activities and therefore provide objective information about motor patterns and activities in the patient's natural environment.

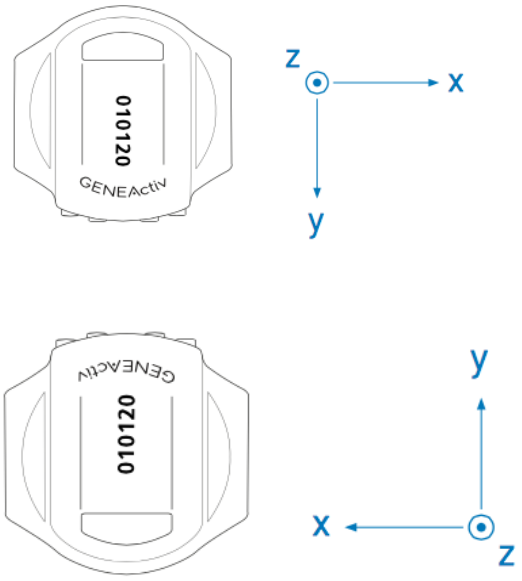

FIGURE 3.5: GENEActive raw data actigraphy device Right-handed [top]; GENEActive raw data actigraphy device Left-handed [bottom] [9].

3.2 Signal Pre-Processing and Features Extraction

The Actigraph sensor is worn by the patient on its most affected wrist and it collects accelerometer data at different sampling frequency: 40 Hz in home monitoring and 100 Hz in V1/V2 visits. The data recorded are related to the motor characterization of the subjects during the whole period of the experiment.

The primary step is to extract the 30 seconds of the accelerometer signals while the BRAIN tests are performed. To ensure a successful extraction of the signal of interest, a window of 40 seconds of sampled data (5s + 30s + 5s) is taken into account (in figure 3.6 are reported samples of the accelerometer signals in X- Y- and Z- axes).

To that end, the temporal information generated by the FitTest (Finger tapping Test - BRAIN test) software are used to pull out, from the packaged accelerometer recording files, the relevant data related to the motor tasks (Python Code - Appendix A - *STEP 1* Data Extraction).

An interval of 20 seconds recording is extracted, from the whole 40 seconds signal, removing the first and the last 10 seconds. The greatest part of the signal information is located in the lower frequency components of the spectrum, up to 20 Hz shown in figure 3.6. So the entire 20s signals are band-pass filtered with a 3 dB cut-off frequency between 0.5 Hz and 20 Hz. The pre-filtering procedure is done to remove artifacts such as noise (electrical power line), gross changes in the orientation of the body segment and, mainly, to remove the zero component (gravity component - position of the Actigraph).

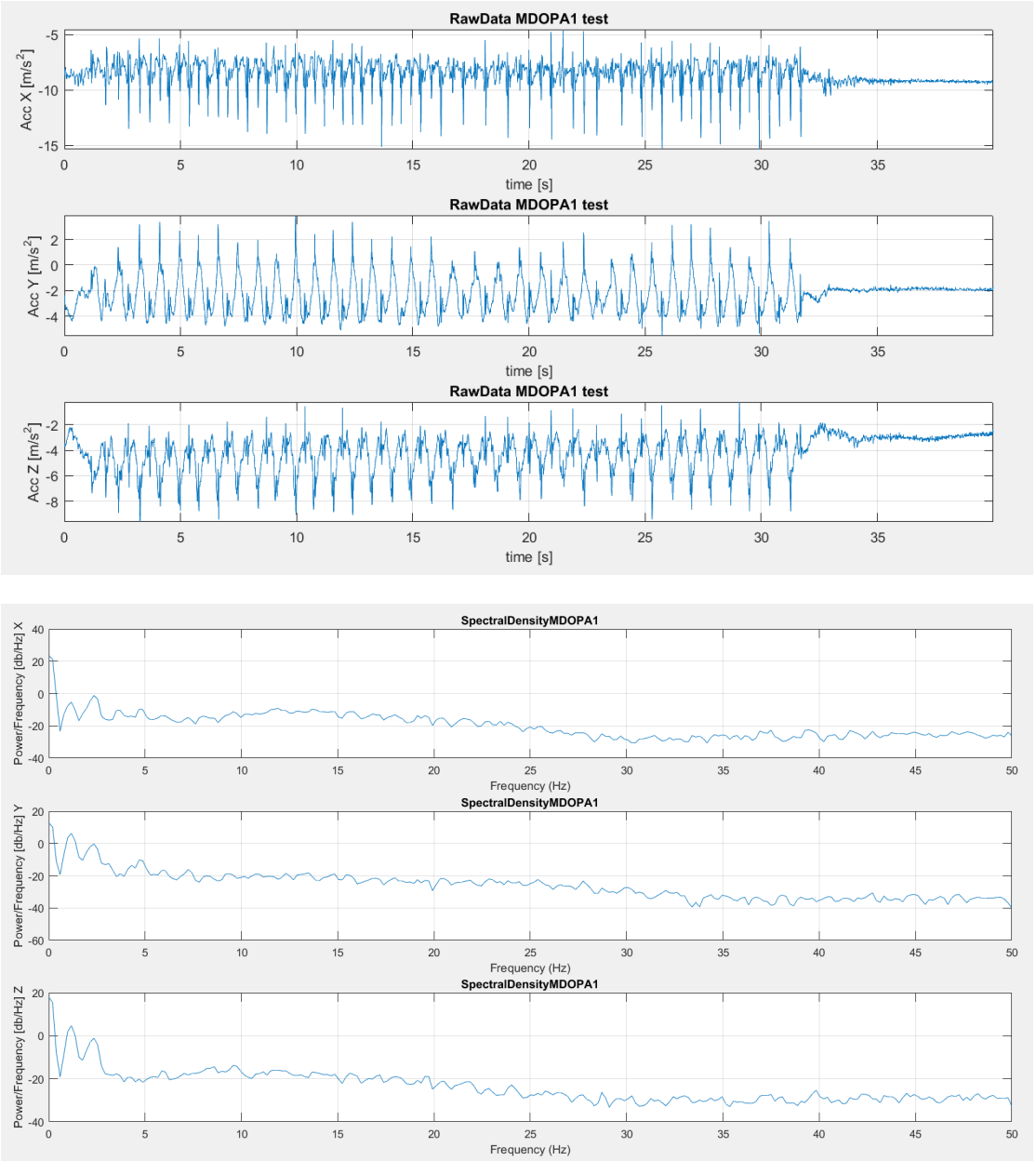

FIGURE 3.6: Accelerometer Actigraph raw data output in X- Y- and Z- axes [top]. Power spectral density PSD of the accelerometer signal in X- Y- and Z- obtained by using Welch's overlapped segment averaging estimator [bottom].

The band-pass filter is realized cascading a second-order Zero-phase digital Butterworth low pass filter and a second-order Zero-phase digital Butterworth high pass filter.
Then, the 20 seconds acceleration data are segmented into several sliding windows. Firstly, it is studied the relevance and the effect of the length of the sliding window on the quantitative analysis of the patient movements. The sampling frequency and the periodicity of the signals are the main parameters which must be taken into account to assume the optimal window's length. At first sight, it had been thought to consider a 10 seconds window, sliding second by second, to obtain an accurate scan of the motor

movement during the whole analyzed task. This choice had proved to be inappropriate as redundant information were extracted from the raw data.
However, the periodicity of the task performed allow us to reduce the window's interval so as to obtain more detailed information of the entire tapping movement. So, finally, a 2 seconds sliding step by step window is used to scan the signal, obtaining a total of 10 characterizing epochs of the 20 seconds recording.

In order to obtain features highly correlated to the characteristics of the motor movements assessed through the MDS-UPDRS, 52 parameters are extracted from each 3-axis accelerometer 2 seconds sliding signal. For each test shall be defined features related to kinetic tremor symptoms and bradykinesia, in addition to features derived merely from the raw accelerometer data.

3.2.1 Raw Data Features

The pre-processed "raw" data are analyzed with the purpose to define a set of dynamic, intensity and periodicity features related to the motor tasks. The attributes may be categorized into temporal and frequency features. Firstly, as temporal feature, the root mean square (RMS $\sqrt{\frac{1}{N}\sum_{n=1}^{N}|x_n|^2}$) is calculated from X- Y- and Z- axes to obtain information related to the intensity of the accelerometer signals. It may be seen as an information of the energy spent by the subject while performing the motor task. The parameter is estimated also for the three-dimensional vector, so to analyze the energy of the movement in a 3D plane.
The dynamic character of the finger tapping task relates to the detection of the amplitude range of the entire movement. For this purpose, the variance and the mean of the signals (*var* function $\frac{1}{N-1}\sum_{i=1}^{N}|x_i-\mu|^2$ where $\mu=\frac{1}{N}\sum_{i=1}^{N}x_i$; *mean* function) are computed for each channel. The dynamic feature is calculated, equally, for the three-dimensional component.
Bearing in mind the Actigraph axes arrangement and the finger tapping movement carried out, it will be justified the main relevance of the X- and Y- components on the results obtained in session *Results and Discussion* during the motor testing analysis.

As regards the spectral attributes, information related to the rate of the movement and the periodicity of the analyzed signal are extracted.
The data are pre-filtered using a second-order Zero-phase digital Butterworth low pass filter with a 3 dB cut-off frequency at 10 Hz. This is because the leading frequency components of the signal are mainly focused in the low frequency part of the spectrum (figure 3.6 power spectra of X- Y- and Z- axes of an M-DOPA+1 test). For that reason it is necessary to remove noisy information that could affect the attributes evaluation.

The Fast Fourier Transform (FFT) of the X-Y-Z- channels and of the accelerometer 3D vector is calculated. The dominant frequency component is figured as the peak frequency (frequency with the maximum power) of the FFT spectra in the range of 0.5 Hz to 10 Hz. The Powers associated to the extracted peaks are also stored. These first parameters are used as descriptors of the task movement rate.
To check that the peaks are likely linked to the desired indicator, the mean normalized frequency value of the power spectrum is computed for the 3-axis and the vector as well. The latter attribute is used to compare its deviation from the peak values calculated previously.

Temporal Raw Data Features	**Frequency Raw Data Features**
RootMeanSquare_X	Peakfrequency_X (0.5-10Hz)
RootMeanSquare_Y	Peakfrequency_Y (0.5-10Hz)
RootMeanSquare_Z	Peakfrequency_Z (0.5-10Hz)
RootMeanSquare_3Dvector	Peakfrequency_3Dvector (0.5-10Hz)
Mean_X	PeakPower_X (0.5-10Hz)
Mean_Y	PeakPower_Y (0.5-10Hz)
Mean_Z	PeakPower_Z (0.5-10Hz)
Mean_3Dvector	PeakPower_3Dvector (0.5-10Hz)
Variance_X	MeanFrequency_X (0.5-10Hz)
Variance_Y	MeanFrequency_Y (0.5-10Hz)
Variance_Z	MeanFrequency_Z (0.5-10Hz)
Variance_3Dvector	MeanFrequency_3Dvector (0.5-10Hz)

Furthermore, with regard to the periodicity information of the accelerometer signal, an additional estimation of the percentage of the ratio of the power associated with the dominant frequency component (computed band - PeakFrequency ±0.1 Hz) to the total power is calculated. This latter attribute is defined for the 3-axes and the 3D vector as well.

Frequency Raw Data Features
Periodicity_X : %(PeakPower±0.1Hz/TotalPower) X_axis
Periodicity_Y : %(PeakPower±0.1Hz/TotalPower) Y_axis
Periodicity_Z : %(PeakPower±0.1Hz/TotalPower) Z_axis
Periodicity_3Dvector : %(PeakPower±0.1Hz/TotalPower) 3Dvector

3.2.2 Tremor Features

The BRAIN test is not really appropriate to assess a resting tremor phenomena, but allow us to extract useful information regarding intention, kinetic and postural tremor events. However as a role, a rest tremor symptom arises in a frequency band in a range

of 4 to 8 Hz, while an action tremor might cover highest frequency components [29]. Therefore, we explored a wider bandwidth applying a second-order Zero-phase digital Butterworth high pass filter with a 3 dB cut-off frequency at 3.5 Hz. The main goal is to detect the frequency component with the highest associated power in the band defined earlier. The Fast Fourier Transform of the accelerometer data is computed. So a research of the maximum value in the power spectrum is done for the X-Y-Z- axes and the 3D spectra. The peak frequency and the power associated are finally stored.
Since the FFT is applied on the 3-axes only, in that case the 3D spectra are computed averaging the spectra of the X-Y-Z- axes. In addition, as done in section 3.2.1, a checking parameter is defined in term of mean normalized frequency value of the power spectra. The last action tremor attribute defined is the percentage of the ratio of the power associated with the dominant frequency component (computed band - PeakFrequency ±0.1 Hz) to the total power. The total power is always linked to the total energy of the spectrum in the range of 1 to 20 Hz.
In the tremor features analysis only frequency attributes are taken into account, since the tremor phenomena is perhaps more clearly evident and detectable in the spectral domain.

Frequency Tremor Features
Peakfrequency_X (3.5-20Hz)
Peakfrequency_Y (3.5-20Hz)
Peakfrequency_Z (3.5-20Hz)
Peakfrequency_3Dvector (3.5-20Hz)
PeakPower_X (3.5-20Hz)
PeakPower_Y (3.5-20Hz)
PeakPower_Z (3.5-20Hz)
PeakPower_3Dvector (3.5-20Hz)
MeanFrequency_X (3.5-20Hz)
MeanFrequency_Y (3.5-20Hz)
MeanFrequency_Z (3.5-20Hz)
MeanFrequency_3Dvector (3.5-20Hz)
PercentagePower_X : %(PeakPower±0.1Hz/TotalPower) X_axis
PercentagePower_Y : %(PeakPower±0.1Hz/TotalPower) Y_axis
PercentagePower_Z : %(PeakPower±0.1Hz/TotalPower) Z_axis
PercentagePower_3Dvector : %(PeakPower±0.1Hz/TotalPower) 3Dvector

3.2.3 Bradykinesia Features

In the analysis of the bradykinesia features extraction, an additional pre-processing filter must be applied. A second-order Zero-phase digital Butterworth low pass filter is used with a 3 dB cut-off frequency at 3.5 Hz. The cut-off component is chosen since

the bradykinesia symptoms regard the slowness of the movement in the motor task performed by the PD patients. In previous works, carried out by Shyamal Patel, Paolo Bonato et al. [28], the low frequency components are the most likely candidates used to analyze the brady-related symptoms; a value of around 3 Hz has been often used.
Once the filtering procedures are done, temporal dynamic velocity features could be extracted from the filtered data. Basically, integrating the acceleration signals the velocity components of the three axes and the velocity 3-dimensional vector are defined.
Hence, the mean and the variance functions are computed in order to estimate kinetic parameters such as the slowness and the entire amplitude range of the movements during the finger tapping tests.

Temporal Bradykinesia Features
VelocityMean_X
VelocityMean_Y
VelocityMean_Z
VelocityMean_3Dvector
VelocityVariance_X
VelocityVariance_Y
VelocityVariance_Z
VelocityVariance_3Dvector

The whole pre-processing and features extraction development methodology is reported in Appendix B - MatLab Code - *STEP 2* Pre-Processing and Features Extraction. The appended code is provided for information purposes only.

3.3 DataSet Construction

The primary goal of the study is to objectively characterize the motor functions of each subject while performing the BRAIN test. Specifically, it could be useful starting to identify the interpersonal variability in the movements of each patient. To that end the 2-week continuous actigraphy recordings are firstly taken into account.
The first dataset assembled is made up of 28 raw data features, 16 tremor features and 8 bradykinesia features. In addition, the day number of the total 14 days and the patient number are included into the dataset.

A further column by the name of "LevoEquivalent" shall be taken into account. The parameter indicates the levodopa equivalent daily dose (LEDD - mg) defined as the sum of all LEDs in a day. The acronym LED means an estimation of the levodopa equivalent dose. The Levodopa Equivalent Dose Calculator is used to compute the contribution made by each of the PD drugs (see drugs table in figure 3.7).

In the following table are reported all the conversion factors paired with each medication. The latter parameter is implemented since the wide variety of drugs, administered to the patients, could have an huge impact factor on the study.

Drug	Conv Factor	Sources and Notes
Amantadine	1	[1]
Apomorphine	10	[1][2] (8/10/8.25)
Azilect	10	Brand name of rasagiline.
Bromocriptine	10	[2]
Cabergoline	80	[2] (66.6/100/80.12)
Duodopa	1.11	[1]*
Entacapone		[1] 0.33*L-Dopa. Enter Levodopa with Entacapone
Levodopa	1	[1]*
LevodopaCR	0.75	[1]*
Levodopa with Entacapone	1.33	Inferred from [1]*.
Levodopa with Tolcapone	1.5	Inferred from [1]*.
Lisuride	100	[2]
Madopar	1	Brand name of levodopa and benserazide.*
Mirapex	100	Brand name of pramipexole
Perglide	100	[2]
Pramipexole	100	[1][2] (67,100,89)
Rasagiline	100	[1] Maximum effect found with 1mg.
Requip	20	Brand name of ropinirole
RequipXL	20	Inferred from [3]. Brand name of ropinirole CR
Ropinirole	20	[1][2] (16.67,33.3,21.3)
RopiniroleCR	20	See RequipXL.
Rotigotine	30	[1]
Rytary	30	Estimate based on [4]*
SelegilineOral	10	[1]
SelegilineSublingual	80	[1]
Sinemet	1	Brand name of levopdopa with carbidopa.*
SinemetCR	0.75	Brand name of controlled release levopdopa with carbidopa.*
Stalevo	1.33	[1][2] (1.2,1.33,1.25)*
Tolcapone		[1] 0.5*L-Dopa. Enter Levodopa with Tolcapone

Note *: This drug contains multiple components. Input the levodopa dose only.

FIGURE 3.7: Drug list and conversion factors used to compute the total LEDD value [10].

The second dataset is set up to find a relationship between the motor functions prediction and the clinical currently used rating parameter MDS-UPDRS.
The MDS-UPDRS-III rating score has been administered in V1 and V2 at the same times of the other assessments (E, M-30 and M-DOPA+1), consequently, the signals recorded in V1 and V2 visits are considered.

In figure C.1 and C.2 - Appendix C - is reported a full filled sample MDS-UPDRS-III test in V1 visit in case of a tremulous patient. The MDS-UPDRS motor examination (part III - 33 items) is employed to assess the objective neurological signs of PD.
Hence, other 6 rating scale test related parameters are included in the second dataset in addition to the standard dataset (raw data attributes, tremor&bradykinesia attributes). The MDS-UPDRS-III total value for each assessment performed is considered. However, since the motor task involve the upper limbs movement of the subject, the clinical items linked to the upper extremities only has been considered (UPDRS_UP 16 items - Table 3.5).

UPDRS_UP
3.3b Rigidity-RUE
3.3c Rigidity-LUE
3.4a Finger tapping - Right hand
3.4b Finger tapping - Left hand
3.5a Hand movements - Right hand
3.5b Hand movements - Left hand
3.6a Pronation/supination - Right hand
3.6b Pronation/supination - Left hand
3.14 Global spontaneity of movement
3.15a Postural tremor - Right hand
3.15b Postural tremor - Left hand
3.16a Kinetic tremor - Right hand
3.16b Kinetic tremor - Left hand
3.17a Rest tremor amplitude - RUE
3.17b Rest tremor amplitude - LUE
3.18 Constancy of rest tremor

Furthermore, the BRAIN motor task does not allow the detection of any kind of rest tremor sign. Recalling that rest tremor can be defined as a rhythmic oscillatory involuntary movement, occurring when the affected body part is not voluntary activated and is completely supported against gravity [42–44], it could be logical to remove the items linked to rest tremor information (UPDRS_UP_kin delete 3.17 to 3.18). In our study no distinction is made between tremor and non-tremor groups.
The analyzed signal is the output of an accelerometer sensor fitted on the mostly affected arm-wrist of the patient. Therefore, to be as accurate as possible in the definition of the target, the clinical rating attribute may be considered as the sum of the values referred to the right or to the left arm only (UPDRS_UP_kin_Affected).

The latter two clinical attributes defined above are expressed also as an exponential pattern (UPDRS_UP_kin_Exp and UPDRS_kin_Affected_Exp). The exponential clinical value is calculated as the sum of the exponential values associated to each of the items.

The exponential target is useful since it replace a weighted sum: the highest severity-values are highlighted in the final sum score. The use of the exponential attribute is inspired by the *"Weber-Fechner Law"*, a ratio-logarithmic-scaling approach. The relationship between the real magnitude and the perceived intensity of a physical stimulus was formulated. In this theory a logarithmic scale perception is supported instead of a linear one [54].

As for the first dataset, information related to the levodopa equivalent daily dose and the matched patient number are added into the V1/V2 related dataset.

The whole dataset construction development methodology is reported in Appendix A - Python Code - *STEP 3* DataSet Construction. The appended code is provided for information purposes only.

3.4 Data Mining

Data mining, also known as data or knowledge discovery, is made up of several quantitative mathematical methods. Data mining may be defined as "the use of automated data analysis techniques to uncover previously undetected relationships among data items" [55]. In other words, it is about analyzing raw data and transforming them into useful information. Machine learning (ML) may be defined as an artificial intelligence able to make multi-dimensional predictions using different analytical tools. Therefore, data mining may be viewed as the application and machine learning as the algorithms used in the implementation.
According to the way the ML algorithms "learn" about data it is possible to split these algorithms into two macro-groups : supervised and unsupervised learning. The first group algorithms aim to predict the output by learning input labelled data; it may be split again into classification and regression problems.
The unsupervised algorithms, in contrast, learn from unlabeled input data to identify elaborated patterns and to define similarity rules. It may be split into clustering and association rule learning problems.

In our case of study, the main goals aim to identify any form of relationship, similarity and/or inter- subject variability of the movements performed. In this scenario the unsupervised machine learning algorithms are the major candidates to compute theses kind of complex processes. Among the different unsupervised machine learning algorithms, the cluster analysis has been considered to be the best choice to make primary qualitative evaluations.

Given the instability of the unsupervised learning techniques, in the final analysis, more stable supervised algorithms could be also used. Particularly, probabilistic classification methods have been used as validation procedures of the unsupervised algorithms results.

Weka Platform. Weka (Waikato Environment for Knowledge Analysis) is a data mining workbench implemented by the University of Waikato (New Zealand, 1997). The open source software is written in Java programming language and it is released under the GNU General Public License.
The software provides facilities such as an interactive GUI that allow us to explore the dataset and to evaluate the analyzed data-output using statistical parameters and visual tools (graphs, tables and curves). In addition, the software has the great advantage of computing and working with big data structures. The mining Weka tool contain a large number of algorithms for classification, clustering, and regression techniques or data pre-processing, features selection methods, finding associations rules and so on.
In the following subsections the clustering and the classification algorithms implemented in Weka, used in the project analysis, will be described in details.

3.4.1 Clustering Methods

A clustering problem is based on the process of grouping events (epochs or instances) into natural clusters, based on similarity criteria. The best cluster analysis is considered to achieve the lowest intra-cluster distance (highest similarity within events collocated in the same group) and the highest inter-cluster distance (disparity between groups).
The clusters may be considered as disjoint sets, that means to take the instances and divide them into sets such that each part of the instance space is in just one cluster - Hard Clustering. The clusters might also overlap, as in overlapping sets, which results in probabilistic assignment techniques of the events to the cluster - Soft Clustering. Moreover, it is possible to have a hierarchical clustering method (dendrogram, classification tree), which could be implemented using agglomerating (bottom up) strategies or divisive (top down) strategies.

In order to compare the results of different clustering algorithms and to evaluate the clustering algorithms themselves, it would be useful to firstly visualize the clusters. In this way it is possible to detect which instances are assigned to each cluster and to extract useful information from the contextualized dataset. In Results and Discussion section it will be explained in details the evaluation procedure in our case of analysis.

In this study disjoint and overlapping clustering techniques are both employed since any a-priori breakdown of the data is given. It may be useful to test the dataset with "hard" and "soft" partitioning clustering techniques as well.

3.4.1.1 K-Means Algorithm

The first algorithm applied on the dataset is the K-means clustering method. It is the simplest unsupervised learning algorithm, and it is based on iterative distance-based clustering (disjoint sets).
K-means algorithm aims to subdivide m events into k a-priori fixed clusters. Firstly, the desired number of k clusters is specified and the algorithm chooses k points randomly as cluster centers. Then, all the instances in the dataset are assigned to their closest cluster center using the Euclidean distance technique. The centroid values are calculated for each cluster as the mean of the instances in it, so that it becomes the new cluster centers. The algorithm carry on iteratively until the cluster center values do not change anymore.
The K-means algorithm minimizes the total squared distance from instances to their cluster centers. Given its simply interpretation and implementation, it presents the advantage to have a lowest running time; moreover it is able to work with high dimensional data. However, the algorithm presents several limits. First of all the hard partitioning method may lead to misgrouping events; in addition, spherical clusters are assumed a-priori (no complex geometrical shaped dataset allowed).
The primary disadvantage taken into account, then tested on Weka to be real, is related to the total squared distance minimization process. The algorithm seeks to research a local minimum instead of a global minimum; different results are achieved setting different random number seeds. In *Results and Discussion* section will be clearly evident the inefficiency of the K-means method on the analyzed dataset.

3.4.1.2 EM - ExpectationMaximization Algorithm

Expectation maximization algorithm is a probabilistic soft clustering method. The basic idea of an EM algorithm arise from a Gaussian mixture model (GMM); the model uses several density probability functions (Gaussian) to pattern the density distribution of the given random data instances. So that each probability distribution is associated with a specific cluster, within which similar behavioural movement events shall be collected. EM could be defined as an iterative method aiming to find the probability distribution parameters (means and covariance matrices) able to maximize a log-likelihood function. To this end two main step are performed (see figure 3.8):

- Expectation step (E): providing an estimate of the probability of each instance to belong to the identified/pre-initialized Cluster $j = 1, 2, ..., N$, an expectation of the log-likelihood function is calculated. The probability value is computed for each x_k event, where k is the total number of features. The log-likelihood function assigns a relevance degree to each event in a class N comparing each element attribute with attributes of elements belonging to C_j clusters. The likelihood function may be seen as a weighted mixture of the Gaussian mixture model.

$$P(C_j|x_k) = \frac{\left|\sum_j(t)\right|^{-\frac{1}{2}} \exp\left(n_j\right) * P_j(t)}{\sum_{k=1}^{N} \left|\sum_j(t)\right|^{-\frac{1}{2}} \exp\left(n_j\right) * P_k(t)}$$

More generally expressed and summarized as the Bayes' Theorem (explained in details in Bayesian Classification section):

$$P(C_j|x_k) = \frac{P(x_k|C_j)P(C_j)}{\sum_{i=1}^{N} P(x_k|C_i)P(C_i)}$$

where the conditional probability $P(x_k|C_j)$ is figured as the multiple Gaussian distribution formula with means and covariance matrices $\sum_j$ of dimension d:

$$P(x_k|C_j) = \frac{1}{\sqrt[d]{(2\pi)\left|\sum_j\right|}} \exp\left[-\frac{1}{2}(x_k - \mu_j)^T * \sum_j{}^{-1} * (x_k - \mu_j)\right]$$

with x_k input dataset, N the total number of clusters and t the instances.
- Maximization step (M): new probability distribution parameters are calculated to maximize the weighted likelihood function found in the previous step. New mean values are computed carrying out the mean of all the instances linked to a specific probability distribution (μ_j - mean of class j); while covariance matrices are iteratively calculated using the Bayesian theorem.

$$P_j(t+1) = \frac{1}{M}\sum_{k=1}^{M} P(C_j|x_k)$$

The probability P_j value associated to each class is computed as the mean of the conditional probability $P(C_j|x_k)$ taking into account the relevance degree. Finally, the M estimated parameter, defining new Gaussian functions, are used in the next expectation step in order to determine the density distribution of the latent variables.

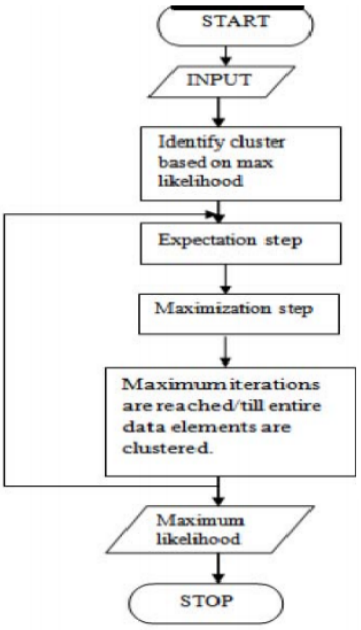

FIGURE 3.8: Flow chart of Expectation - Maximization Algorithm in Weka.

Compared to the K-means clustering algorithm the main advantage of an EM algorithm is that it gives the chance whether or not to decide a-priori the number of N-clusters. So that it is possible to boost an additional degree of freedom in the clustering process. In Weka the algorithm decides the number of clusters to be created using a cross validation technique:

1. the number N of clusters is set to one;
2. the data used to train the clustering algorithm are split randomly in ten folds;
3. the algorithm is performed ten times implementing the classical Cross-Validation technique using the ten folds;
4. the log-likelihood values obtained from the ten runs are averaged;
5. in case of a log-likelihood value larger than previous one, the number of clusters is increased by 1 and the algorithm restart from point 2; otherwise the number of clusters are achieved stopping the research process.

Mathematically, in order to search the maximum log-likelihood value, the Gaussian mixture model takes into account the variance values implementing the covariance matrices step by step; otherwise, K-means algorithm limits the analysis on a simple conventional Euclidean distance calculation. So the mixture models may be interpreted as a generalization of K-means clustering techniques. Additionally, both use iterative cluster center values to pattern the data, but while K-means clustering tends to assume a specific cluster geometry (spherical), the EM algorithm is able to work with elliptic shape clusters (iterative moulding) using non-linear geometric distributions.

3.4.2 Classification Methods

A classification problem involves predicting whether given observation belongs to a certain category or class. Based on earlier observations of how the input maps to the output, classification tries to estimate a classifier that can generate an output for an arbitrary input. The classifier can then label an unseen instance with a specific class basing on the classification rules previously defined.
Therefore, the classifier may be seen as a predictor function $y = f(x)$ able to make predictions y about the input data x. The predictions y are a finite-discrete and, usually, small number of classes; the x is the representation of the input data expressed in term of k values of attributes. There exist several learning methods related to the classification problem basing on similarity functions (e.g. k-Nearest Neighbours), frequency table based classifiers (e.g. ZeroR, OneR, Decision Tree), probabilistic classifiers (e.g. Naive Bayes), linear decision boundary and so on.
The following study will focus particularly on the category of the probabilistic classifiers. The probabilistic classifiers basically predict the class basing on the computed probability of that class. This means that the classifier first predicts the probability and then pick the class that has the highest probability given the observation.

3.4.2.1 Bayesian Classification

The Bayesian classification technique is a probabilistic based classifier and it has been chosen in our study as it is based on the Bayes' Theorem, also used in the previous EM clustering problem.

$$P(C_j|x_k) = \frac{P(x_k|C_j)P(C_j)}{\sum_{i=1}^{N} P(x_k|C_i)P(C_i)}$$

$P(C_j)$ is the prior probability of a class j independently from the given input; it is the baseline probability of the event before any evidence x_k (attribute values of an unknown instance) is explored. $P(x_k|C_j)$ is named the class-conditional model, assuming that the output is in C_j class describes how likely to see observation x_k in class C_j.
Then, the sum over all the classes, in the bottom of the formula, does not usually affect the classification. The whole expression may be considered as the same thing as $P(x_k)$, which is the prior probability of a set of observation unconnected to any class, a constant value.

Therefore, the denominator does not actually affect the entire prediction as it is not connected to any class. However, the whole sum expression is reported in the formula as it could be useful to rank the instances x_k by the probability that they are classified in the C_i class.

Naive Bayes Classifier in Weka. Naive Bayes is a specif sub-type of a Bayesian classifier, where the Bayesian classifiers themselves are part of the family of the probabilistic classifiers. Naive Bayes may be considered as a generative model as it computes predictions by modeling each class, not just looking the boundaries. The Naive Bayes classifier is clearly based on the Bayes' Theorem.
Hence, the posterior probability of a hypothesis C_j given evidence x_k is estimated. The "naive" assumption is that the evidence splits into attributes that are statistically independent. Where the attributes of the evidence in our case are the 52 different feature values in the datatset. So, assuming the events to be independent, the class-conditional model probability (class conditional independence) may be expressed as follow:

$$P(x_k|C_j) = P(x_1|C_j) * P(x_2|C_j) * P(x_3|C_j) * ... * P(x_k|C_j)$$

to finally obtain, by replacing the denominator constant value as discussed earlier:

$$P(C_j|x_k) = \frac{P(x_1|C_j) * P(x_2|C_j) * P(x_3|C_j) * ... * P(x_k|C_j)P(C_j)}{P(x_k)}$$

Therefore, the main assumption is that all the attributes contribute equally and independently to the outcomes. Nevertheless, the Naive Bayes algorithm works surprisingly well even though the independence assumption, as in our dataset, is clearly violated. This could be explained considering that, basically, the classification technique does not need accurate probability estimates. The algorithm are just predicting as the class the outcomes with the largest probability. Hence, as long as the greatest probability is assigned to the correct class, it could be irrelevant that the probability estimates are all that accurate.

However, in general, working with redundant attributes the Naive Bayes classifier may cause problems during the Training procedure. So a pre-feature selection procedure has been considered to be necessary to allow us to select a subset of fairly independent attribute. The Correlation-based Feature Selection has been chosen.
In Weka the Correlation-based Feature Selection Subset Evaluation (CfsSubsetEval) is computed as a scheme-independent attribute subset evaluator. It integrate an attribute subset evaluator with some search methods as to allow us to eliminate the redundant

features as well as irrelevant ones. The method considers an attribute subset to be good if the attributes are correlated with the class feature, and not closely correlated with one another. The Cfs method is based on a measure of the "goodness" of the subset parameters:

$$Goodness = \frac{\sum_{all\_attributes\_k} C(x_k, C_j)}{\sqrt{\sum_{all\_attributes\_k} \sum_{all\_attributes\_k'} C(x_k, x'_k)}}$$

In the formula the sum of the correlation C between the attributes and the class is computed over all of the attributes in the subset; then all is divided by square root of the correlations of each attribute with each other attribute, summed over all pairs of attributes. As regards the correlation parameter, the CfsSubsetEval method uses an entropy-based metric known as "symmetric uncertainty" described and discussed in details in Mark A. Hall thesis [56].

Chapter 4

Results and Discussion

The whole study has been carried out with the aim to create an algorithm able to estimate an inter- variability of the patients motor functions, and able to detect patients groups in correlation with the MDS-UPDRS clinical score.
Firstly, statistical methods are applied on the dataset constructed through the 40 Hz weekly home monitoring recordings. These tests are done to try to define an inter–variability between different subjects performing the same motor task.
The need to validate the algorithm on clinical guidelines leads to shift the analysis on the second dataset constructed. In this phase the validation tests are performed on the 100 Hz V1 and V2 visits recordings.
The following analysis are done considering the motor task performed only in the morning one hour after the first dopaminergic drug intake (M-DOPA+1). This is done because, in this way, it may be easier to control the several effects of the medications on the subjects movements. Indeed, hereafter none of the results achieved in M-30, A-DOPA and E sessions will be reported. In these latter tests conditions, the patients may be in different stages of drug release and assumption process; the construction of an algorithm, PD motor detector, could be compromised by drug related factors.
In addition, none of the results obtained considering the levodopa equivalent daily dose as a classification parameter will be shown. This is because the parameter is specifically associated to the single patient; so the levodopa equivalent daily dose attribute may be interpreted, by the classification algorithms, as an identification number (ID) of the specific subject, compromising the whole prediction.

4.1 Sleep & Move Home-monitoring

In this section are figured the results obtained performing the clustering and the classification techniques on the 2 weeks dataset recordings, considering, only, the 52 extracted motor features. The analysis will be unrelated to any clinical validation parameter, as no clinical assessment has been carried out during the home monitoring tasks.
In figure 4.1 and 4.2 are plotted the results of K-means and EM Weka algorithms, presetting the k clusters number equal to the total number of patients in exam. This is done to verify if the algorithm is able to detect an inter- variability between the different subjects. The graphs show for each patient (x-axis) and for each day (y-axis) the cluster in which a specif 2 second epoch-recording is grouped. Each of the k clusters are coded with different k colours.

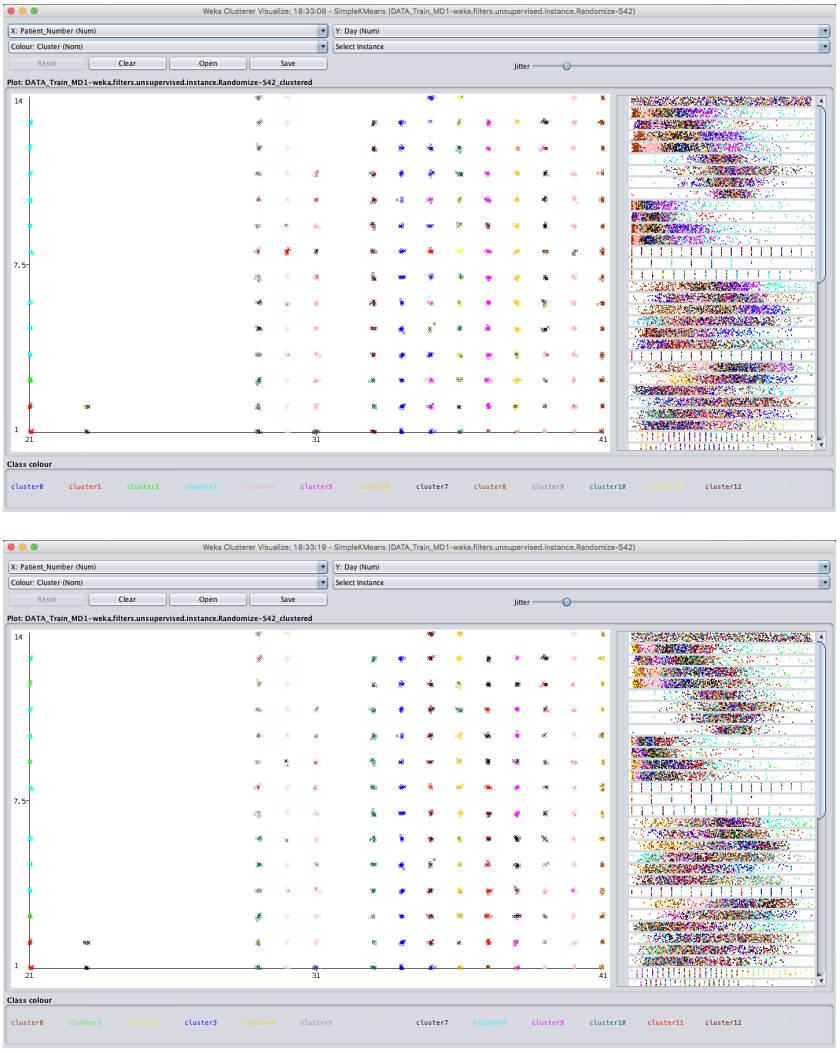

FIGURE 4.1: K-means algorithm with k equal to a number of 14 clusters; as an example two random running seeds reported : [top] seed value 10, [bottom] seed value 50.

In order to test the performance and the stability of the two clustering algorithms, different seed values are used. It is clearly evident how different seed numbers produce totally changed outcomes in K-means algorithm (figure 4.1 [top] & [bottom]). On the other hand, in EM technique slighter outcomes variations are achieved using different seed values (figure 4.2 [top] & [bottom]).
In the analysis of the results obtained with the EM algorithm, an inter- variability between different subjects is detected. Every patient is nearly paired with a specif colour. Note that, in both graphs, no data are available in patients for whom errors in sensor recording processes have been done (patients SAM022, SAM024-SAM028 and SAM032). In addition, not everybody have played their daily M-DOPA+1 session motor task.

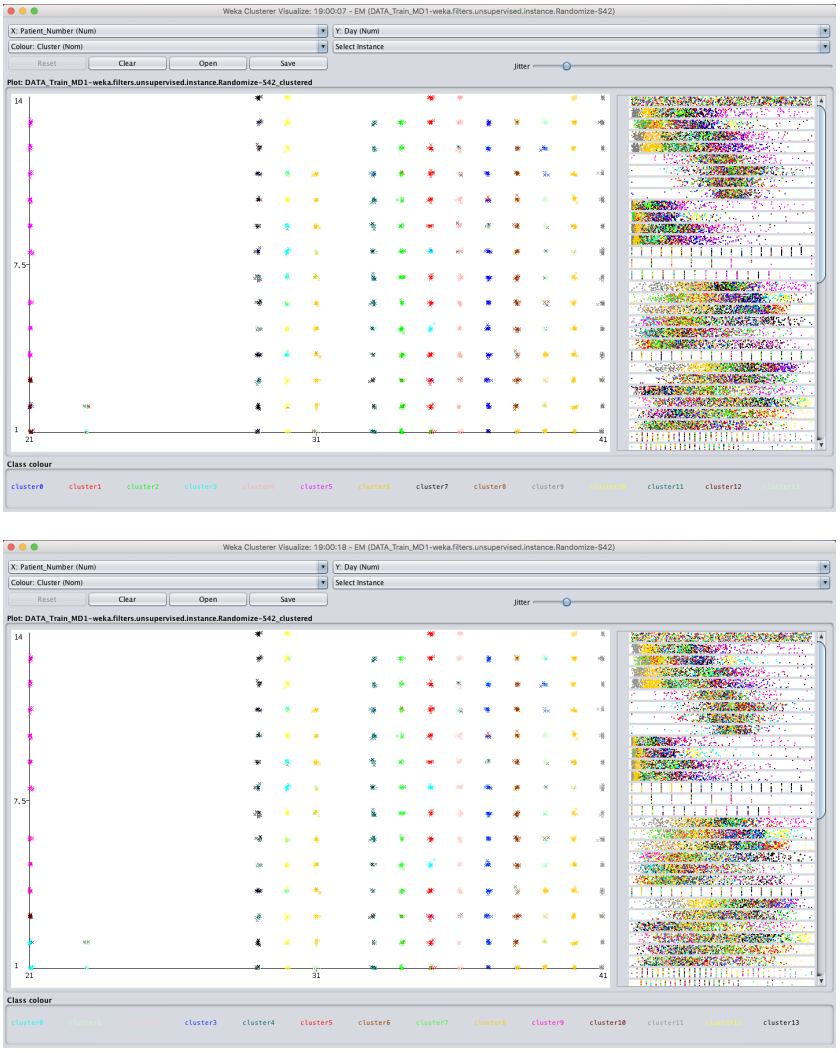

FIGURE 4.2: EM algorithm with k equal to a number of 14 clusters; as an example two random running seeds reported : [top] seed value 50, [bottom] seed value 70.

Thanks to Weka graphic "Visualize" tools, shown in figure 4.3, has been checked the characteristic of overlap of the data in d dimensions. So, given the overlapping data, some subjects may be clustered in two or more groups. It may be a primary evidence of an intra- patient variability while performing the same motor task.

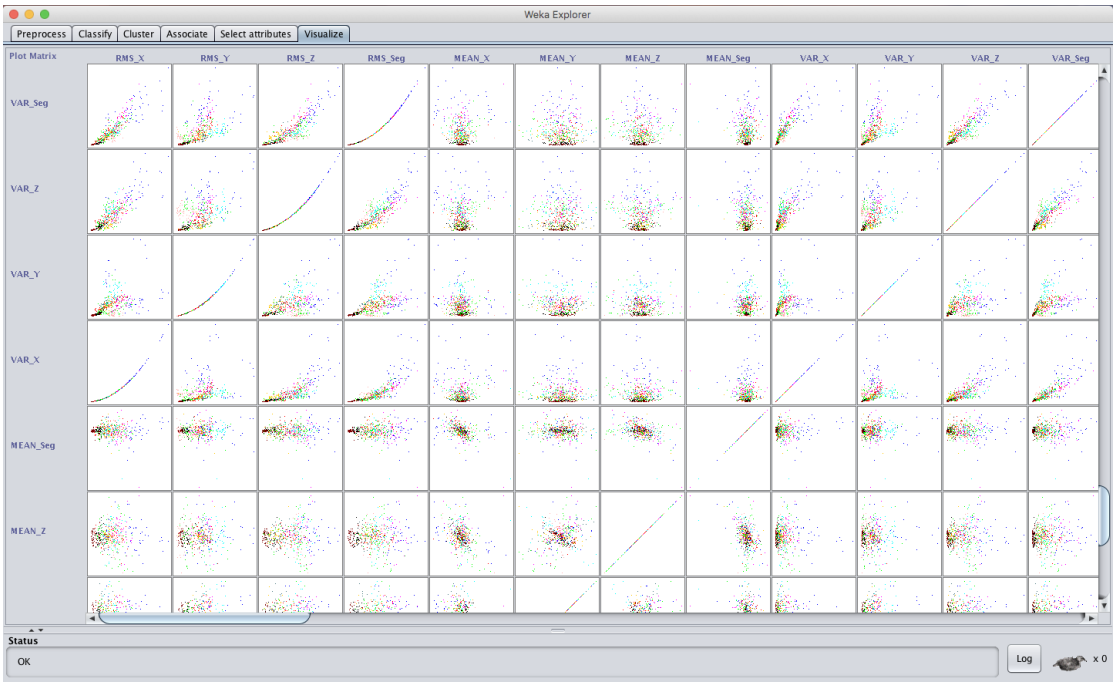

FIGURE 4.3: A glimpse of the 52x52 d dimensions features matrix. Each graph/cell of the matrix allow to analyze and visualize the data distribution linked to each patient (coded by a specific colour) given the labelled features.

But over and above K-means limits, these results may be decoded as the necessity to use an algorithm able to work with overlapping data. From here on out, all the analysis will be performed using the more stable mixture model based algorithm.
Moreover, the rules on which the clustering algorithms are based, seem to be linked mainly to the movements taking place in X-Y- plane. In figure 4.4 an example of dataset distribution plotted as function of x-axis and y-axis temporal features is showed. In particular, the graphs are set out, as an example, in function of RMS_X and VAR_Y parameters and vice-versa (RMS_Y and VAR_X). Despite the constant overlap, almost clear division boundaries appear to be identified by the algorithm (coloured area in figure 4.4). Other grouping correlation rules are thought to be identified linked to frequencies features distribution too. This latter assessment will be explained by the resulting frequency selection outcomes shown up ahead in the following section.

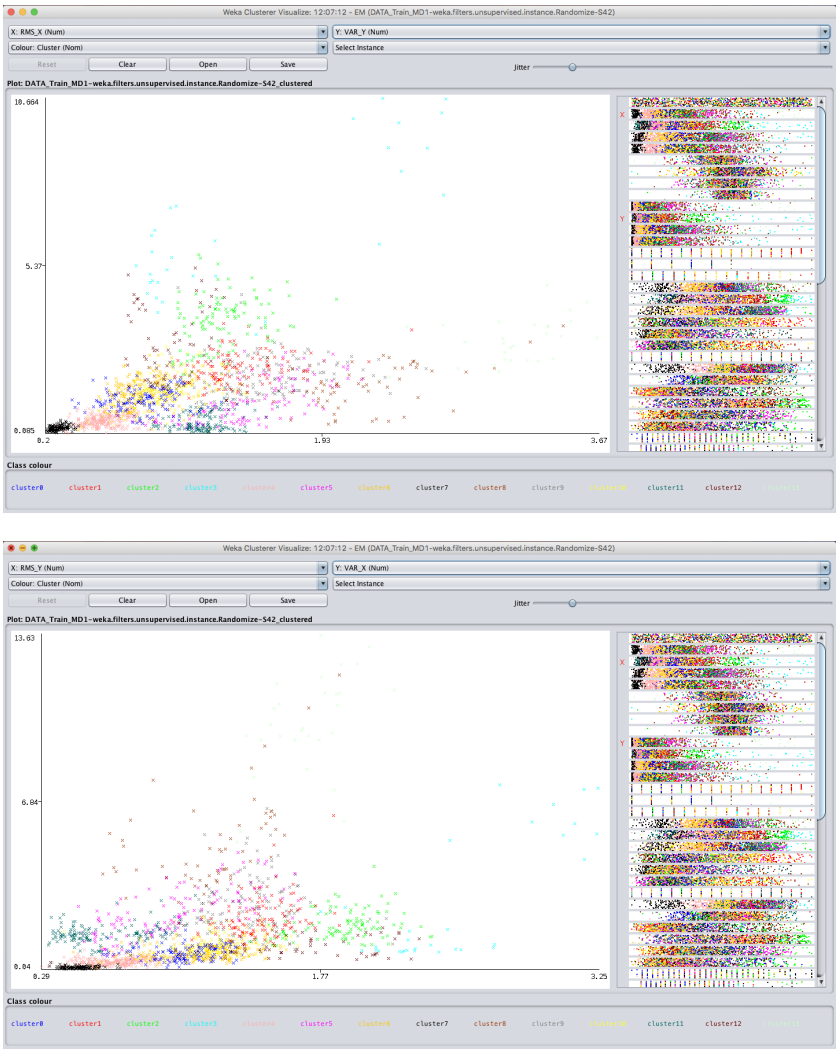

FIGURE 4.4: EM algorithm with k equal to a number of 14 coloured clusters and random seed value. Dataset distribution in X-Y plane function of RMS_X feature against VAR_Y feature [top] and vice-versa (RMS_Y against VAR_X) [bottom].

The results and the above evaluations are shown basing on the outcomes of clustering techniques only. Irrespectively of whether the EM clustering algorithms could be considered "stable", the seed parameter affects the results, changing sometimes the grouping processes, also just a tick.

Hence, additional tests are done by using the probabilistic Naive Bayes classifier. The classification algorithm is performed to verify and to validate the ability to detect the inter–personal variability between different subjects.

Always basing on the 52 motor features extracted, the targets that the classifier has to predict are the patients themselves. Firstly, the dataset is divided into *training set* and *test set*. The *training set* is made up of the dataset information collected during the 14 days not considering the data related to the tasks performed during the first day. The data instances of the tasks performed in the first day shall be the *test set*.

The labels that the classifier has to predict are the 12 patients. The patients SAM023

and SAM031 are deleted as they do not perform all the M-DOPA+1 daily task. In addition, in order to balance the dataset, the analysis are done considering 12 days, only, since not everybody has performed the motor task in the days 7 and 14.

In figure 4.5 are shown the statistical results of the Naive Bayes classification method applied on the *training set* in a stratified k=10 cross-validation testing mode. A percentage of about 88.56% of correctly classified instances is achieved. In addition, the mean accuracy value with its standard deviation $88.47\% \pm 2.70$ (resulting from 10 repetition of the algorithm performed in the *Experimenter* environment in Weka) is given inside the outer blue border. Therefore, the obtained statistical measures prove that the algorithm, paired with the extracted characterizing features, is able to recognize an inter- variability of the movements of different subjects.

```
=== Summary ===

Correctly Classified Instances        1169               88.5606 %
Incorrectly Classified Instances       151               11.4394 %
Kappa statistic                          0.8752
Mean absolute error                      0.0198
Root mean squared error                  0.132
Relative absolute error                 12.9537 %
Root relative squared error             47.7664 %
Total Number of Instances             1320

=== Detailed Accuracy By Class ===

               TP Rate   FP Rate   Precision   Recall  F-Measure  MCC      ROC Area  PRC Area  Class
               0,982     0,008     0,915       0,982   0,947      0,943    0,986     0,949     21
               0,791     0,010     0,879       0,791   0,833      0,820    0,967     0,886     29
               0,936     0,015     0,851       0,936   0,892      0,883    0,984     0,946     30
               0,827     0,019     0,798       0,827   0,813      0,795    0,983     0,909     33
               0,945     0,002     0,972       0,945   0,959      0,955    0,989     0,972     34
               0,782     0,012     0,851       0,782   0,815      0,800    0,970     0,813     35
               0,909     0,014     0,855       0,909   0,881      0,870    0,988     0,941     36
               0,882     0,007     0,915       0,882   0,898      0,889    0,996     0,966     37
               0,918     0,008     0,910       0,918   0,914      0,906    0,995     0,933     38
               0,718     0,012     0,840       0,718   0,775      0,758    0,972     0,864     39
               0,945     0,014     0,860       0,945   0,900      0,892    0,988     0,960     40
               0,991     0,002     0,982       0,991   0,986      0,985    1,000     0,990     41
Weighted Avg.  0,886     0,010     0,886       0,886   0,884      0,875    0,985     0,927

=== Confusion Matrix ===

   a   b   c   d   e   f   g   h   i   j   k   l   <-- classified as
 108   1   0   0   0   1   0   0   0   0   0   0 |   a = 21
   3  87   0   9   0   0   6   0   0   5   0   0 |   b = 29
   2   0 103   0   0   3   0   1   1   0   0   0 |   c = 30
   0   9   0  91   0   1   6   0   0   3   0   0 |   d = 33
   1   0   0   0 104   4   0   1   0   0   0   0 |   e = 34
   3   1  17   0   0  86   0   2   0   1   0   0 |   f = 35
   0   1   0   6   0   0 100   0   0   2   1   0 |   g = 36
   1   0   0   0   3   5   0  97   2   2   0   0 |   h = 37
   0   0   1   0   0   0   2   1 101   0   5   0 |   i = 38
   0   0   0   8   0   1   3   4   4  79  10   1 |   j = 39
   0   0   0   0   0   0   0   0   3   2 104   1 |   k = 40
   0   0   0   0   0   0   0   0   0   0   1 109 |   l = 41
```

```
Dataset                    (1) meta.AttributeSe
-----------------------------------------------
DATA_Train_MD1-weka.filte(100)   88.47(2.70)
-----------------------------------------------
(v/ /*)                                      |
```

FIGURE 4.5: Performance statistical measures of the Naive Bayes classifier applied on the 2 weeks *training set* - without the first day recordings - in 10 cross-validation testing mode. A summary of the evaluation parameters and the detailed accuracy values by class are reported, in addition with the confusion matrix table.

An additional test is done training, previously, the Naive Bayes classifier on the *training set*, then testing the classifier on the *test set* defined above. In figure 4.6 the statistical results are provided. Although the percentage of correctly classified instances can be still considered good, since a total accuracy of 74.17% is achieved. The results show a primary evidence of similarities of the movements between different subjects (e.g. Class j - patient_SAM039 - with 90% similarity with class k - patient_SAM040, see Confusion Matrix in figure 4.6).

```
=== Summary ===

Correctly Classified Instances          89               74.1667 %
Incorrectly Classified Instances        31               25.8333 %
Kappa statistic                          0.7182
Mean absolute error                      0.042
Root mean squared error                  0.1981
Relative absolute error                 27.482  %
Root relative squared error             71.6746 %
Total Number of Instances              120

=== Detailed Accuracy By Class ===

                 TP Rate  FP Rate  Precision  Recall   F-Measure  MCC      ROC Area  PRC Area  Class
                 0,900    0,009    0,900      0,900    0,900      0,891    0,991     0,798     21
                 0,800    0,055    0,571      0,800    0,667      0,642    0,964     0,599     29
                 1,000    0,009    0,909      1,000    0,952      0,949    0,997     0,970     30
                 0,800    0,000    1,000      0,800    0,889      0,886    1,000     1,000     33
                 1,000    0,045    0,667      1,000    0,800      0,798    0,994     0,927     34
                 0,500    0,000    1,000      0,500    0,667      0,692    0,978     0,875     35
                 1,000    0,000    1,000      1,000    1,000      1,000    1,000     1,000     36
                 0,400    0,000    1,000      0,400    0,571      0,616    0,885     0,811     37
                 0,400    0,000    1,000      0,400    0,571      0,616    0,959     0,851     38
                 0,100    0,027    0,250      0,100    0,143      0,112    0,924     0,416     39
                 1,000    0,127    0,417      1,000    0,588      0,603    0,998     0,983     40
                 1,000    0,009    0,909      1,000    0,952      0,949    0,999     0,991     41
Weighted Avg.    0,742    0,023    0,802      0,742    0,725      0,729    0,974     0,852

=== Confusion Matrix ===

  a  b  c  d  e  f  g  h  i  j  k  l   <-- classified as
  9  0  1  0  0  0  0  0  0  0  0  0 |  a = 21
  0  8  0  0  0  0  0  0  0  2  0  0 |  b = 29
  0  0 10  0  0  0  0  0  0  0  0  0 |  c = 30
  0  1  0  8  0  0  0  0  0  1  0  0 |  d = 33
  0  0  0  0 10  0  0  0  0  0  0  0 |  e = 34
  0  0  0  0  5  5  0  0  0  0  0  0 |  f = 35
  0  0  0  0  0  0 10  0  0  0  0  0 |  g = 36
  1  5  0  0  0  0  0  4  0  0  0  0 |  h = 37
  0  0  0  0  0  0  0  0  4  0  5  1 |  i = 38
  0  0  0  0  0  0  0  0  0  1  9  0 |  j = 39
  0  0  0  0  0  0  0  0  0  0 10  0 |  k = 40
  0  0  0  0  0  0  0  0  0  0  0 10 |  l = 41
```

FIGURE 4.6: Performance statistical measures of the Naive Bayes classifier applied on the *test set* - first day recordings - in testing mode, training the algorithm on 2 weeks *training set* - without the first day recordings. A summary of the evaluation parameters and the detailed accuracy values by class are reported, in addition with the confusion matrix table.

The Naive Bayes classification procedures, k=10 cross-validation testing mode and splitting Train/Test mode, are performed on several *training set* and *test set*. These latter dataset are created removing, as above, one day data recordings for all examined patients at time. The data removed shall be considered as the *test set* and the remaining part

as *training set*. In the following table are reported the performance statistical accuracy measures of the all conducted tests.

Training Set & Test Set	**Cross-Validation Testing mode**	***Experimenter* Cross-Validation**	**Split Train/Test Testing mode**
deleting 1st day	88.56%	$88.47\% \pm 2.70$	74.17%
deleting 2nd day	87.65%	$88.06\% \pm 2.48$	80.00%
deleting 3rd day	88.18%	$88.42\% \pm 2.48$	71.67%
deleting 4th day	88.79%	$88.36\% \pm 2.63$	81.67%
deleting 5th day	89.01%	$88.66\% \pm 2.58$	79.17%
deleting 6th day	87.73%	$87.48\% \pm 2.67$	93.33%
deleting 8th day	88.26%	$88.12\% \pm 2.78$	79.17%
deleting 9th day	88.18%	$88.21\% \pm 2.65$	86.67%
deleting 10th day	87.04%	$87.11\% \pm 2.57$	92.50%
deleting 11th day	87.88%	$87.47\% \pm 2.70$	85.00%
deleting 12th day	88.11%	$87.95\% \pm 2.59$	85.00%
deleting 13th day	87.88%	$87.48\% \pm 2.82$	89.17%

Furthermore, the algorithms have been tested performing the CfsSubsetEval feature selection. The redundant and irrelevant features are marked (red tag) in order to point out the attributes assuming the grater weight during the motor classification processes. In figures C.3 and C.3 - Appendix C - are reported the outcomes of the feature frequency table resulting from the performance of CfsSubsetEval algorithm.

4.2 Awake & Move V1 and V2 visits

The analysis carried out during V1 and V2 visits are done to find relationships between the estimates of the motor task grouping techniques and the clinical rating scores. The main limit is given by the lack of a consistent disease evaluation method. MDS-UPDRS-III objective motor evaluations are done by two different neurologists in V1 and V2 visits, even switching each other from one patient to the other. Hence, if normally small fluctuations in terms of UPDRS value may be assumed for the same subject, now the probability to store a larger value's variability increase.
Even though the clinical rating scale is considered to be an objective assessment, there is still a subjective neurologist evaluation influence on the final score. The forthcoming analysis will concern only the test performed during V2 visit, since the clinical evaluations are supposed to be done by the same neurologist.
As in home monitoring tasks, a primary check is done to identify an inter- variability between the patients. K-means and EM have been tested both to verify the greater stability of the Gaussian mixture based model.

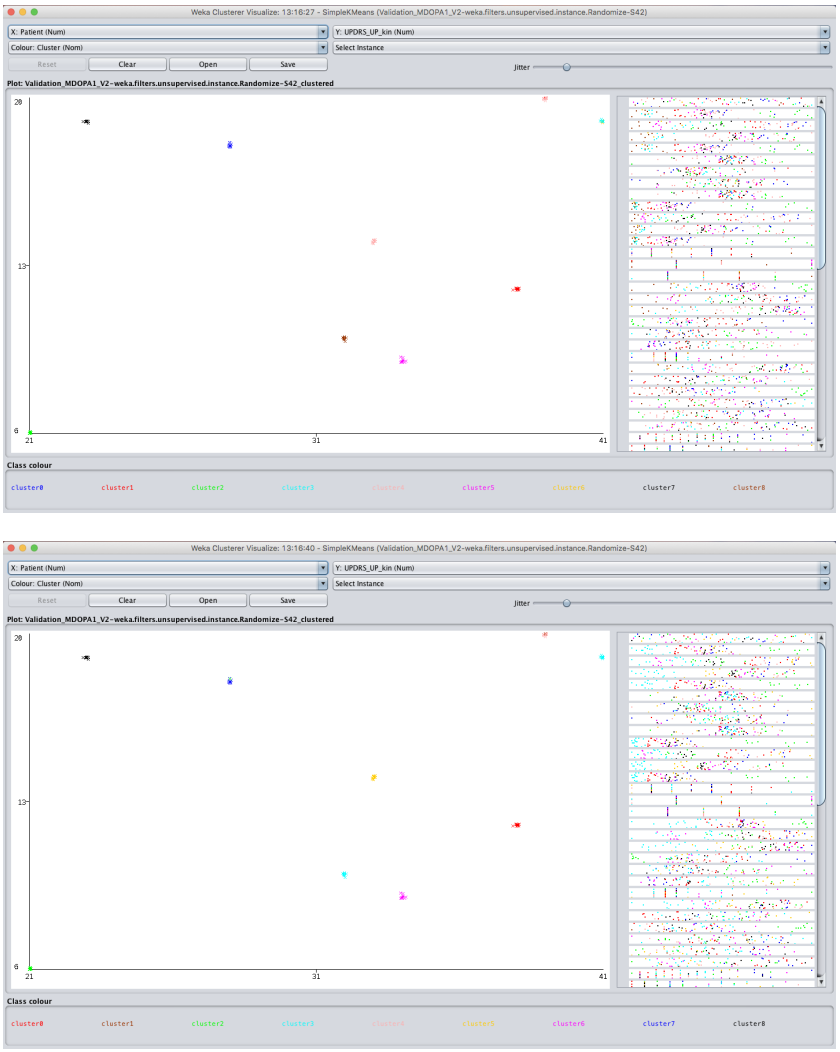

FIGURE 4.7: K-means algorithm with k equal to a number of 9 clusters; as an example two random running seeds reported : [top] seed value 10, [bottom] seed value 60.

Different seed numbers are used; the k value is pre-set equal to the total number of the patients in exam. In figure 4.7 and 4.8 the graphs show each patient (x-axis) matched with its clinical UPDRS_UP_kin score (y-axis), and the cluster in which the 2-second epochs are grouped. Each of the k clusters are coded with different k colours.
The results confirm the previous home monitoring tests findings, that is the totally changed output in K-means algorithm compared to the tiniest fluctuations of the EM technique. As regard the mixture model results, a variability inter- subjects is identified since each patient is paired with a specific colour. In the graphs no data are available for all patients, since the secondary Awake & Move study has been conducted on a subgroup of consecutive unselected PD subjects.

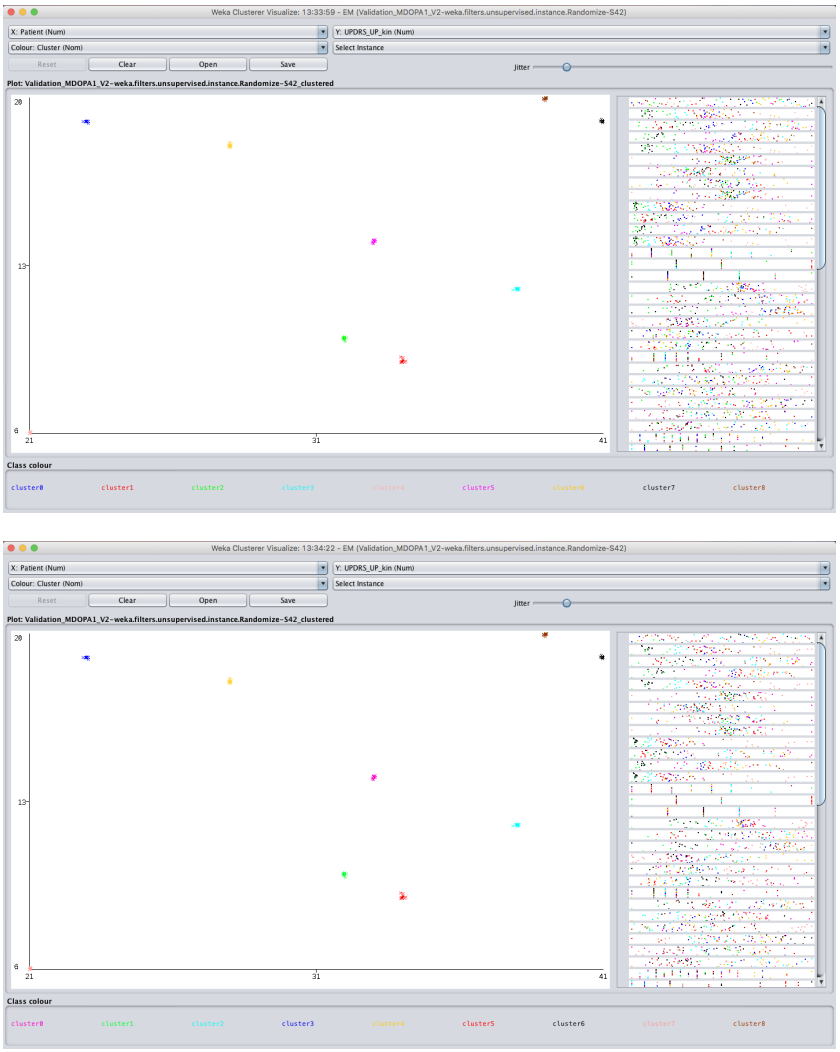

FIGURE 4.8: EM algorithm with k equal to a number of 9 clusters; as an example two random running seeds reported : [top] seed value 50, [bottom] seed value 80.

In order to test a primary relationship between the UPDRS score and the motor characters of the different subjects, the chance to not choose the k value a-priori in EM algorithm is exploited. In figure 4.9 the graph displays each patient (x-axis) paired with its clinical UPDRS_UP_kin_Exp score (y-axis), and the coloured decoded cluster in which is placed. In the following and for the next clinical evaluation the use of the "Exp" value is preferred as the reason explained in *dataset Construction* section.
Overall, the graph shows five clusters, at first sight disposed in five different band of UPDRS exponential values. Except for the patient SAM041, the subjects with similar values of UPDRS_UP_kin_Exp seem to be grouped in the same coloured cluster.
Even for SAM033 and SAM038 a little discrepancy is figured as these two patients are collocated in two different cluster colour. It may be assumed that this discrepancy is the result of a tight similarity of their motor functions.

In addition, in contrast to what was said during the UPDRS visits, the results of any analysis carried out, from now on, recognize a similarity between the patient SAM032 and SAM041.

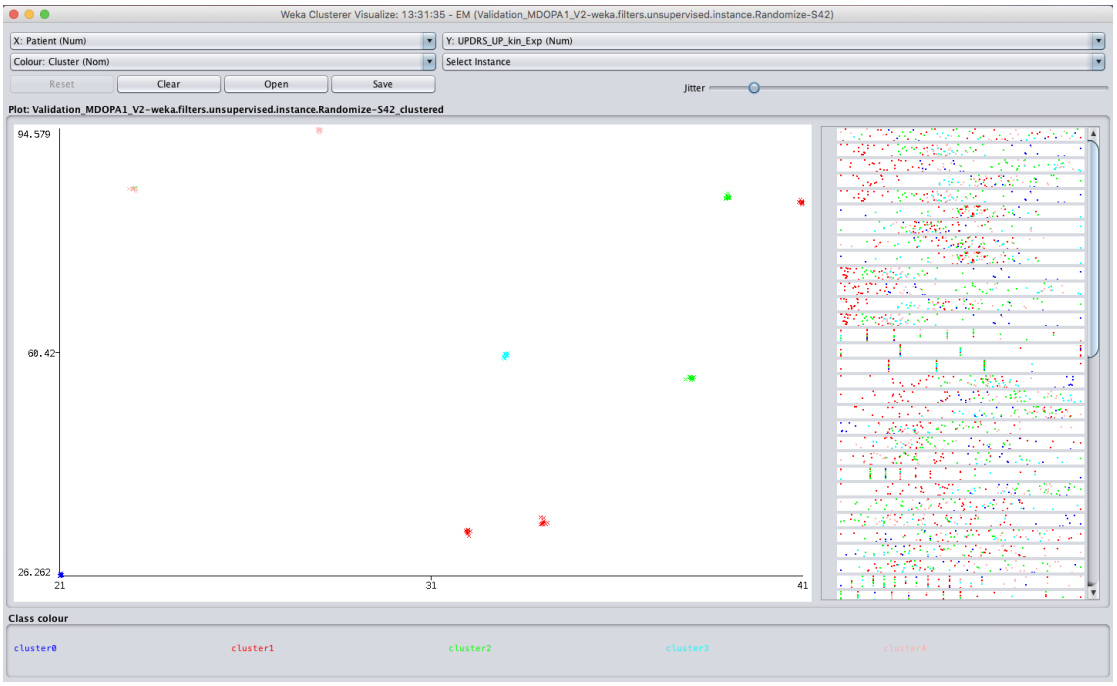

FIGURE 4.9: EM algorithm with k equal to a number of undefined (-1) clusters, it means no a-priori restriction on cluster numbers is given.

The data distribution shown in figure 4.9 is related to the maximum log-likelihood value obtained among the different seed numbers tested. The maximum log-likelihood value means defining the lowest intra-cluster distance and the highest inter-cluster distance. And what is more, an higher likelihood value imply the identification of a lower number of cluster. Hence, care should be taken to find a good compromise in term of number of cluster identified against the better log-likelihood achieved.
Then, further tests are done setting k a-priori values lower than the value obtained in the $k = -1$ configuration. In figure 4.10 the graphs show the resulting groups identified setting k equal to 3 and k equal to 4 number of clusters. The graphs figure each patient (x-axis) paired with its clinical score UPDRS_UP_kin_Exp score (y-axis) and the group in which it is clustered. By reducing the k clusters value, it is evident how the patients with similar clinical scores, UPDRS_UP_kin_Exp, are grouped in the same coloured cluster. So a primary important results is achieved identifying a correlation between the UPDRS international guideline scoring method and the motor grouping techniques findings. It is also recalled, as in the previous $k = -1$, the similarity resulting in SAM032 and SAM041 patients as opposed to the different clinical score reported by the neurologists.

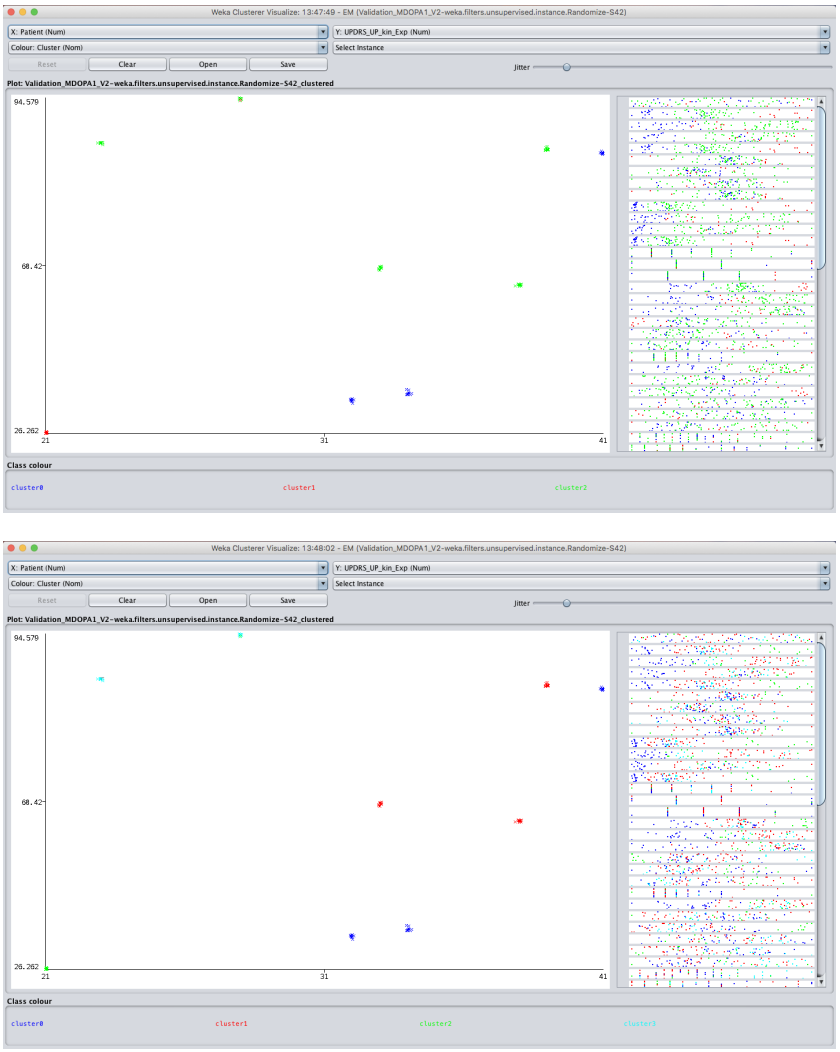

FIGURE 4.10: EM algorithm with k equal to a number of 3 clusters [top], and k equal to a number of 4 clusters [bottom].

In the light of the obtained outcomes, it should be noted that the UPDRS_UP_kin or UPDRS_UP_kin_Exp clinical parameters have been used instead of the UPDRS_UP_kin_Affected one. This latter choice stems from different evaluations, chief among which is the consideration that the not affected side may influence, somehow, the motor task's performance. Also, the additional advantage in using the UPDRS_UP_kin or exponential scoring methods is the chance to validate the algorithm on a larger scale, that means working on a wider range of values.

As done in home-monitoring analysis, further validation studies are performed using the Bayesian classification algorithm. The classification is carried out considering the dataset extracted in V1 and in V2 visits, using the V1-data as training set and V2-data as test set and vice-versa. The targets that the classifier has to predict are the subjects themselves. In the following analysis, the number of patients has drastically decreased; this is because only 7 subjects have performed the M-DOPA+1 motor task in V1 and V2 visits both.
In figure 4.11 is reported the resulting confusion matrix of the Naive Bayes classifier trained using the V1-data and tested on the V2-data. On the basis of the tasks performed during the V1 visits, the test results show that the classification algorithm is not able to recognize the individual patient. However, much more interesting, several groups may be identified since different subjects have been classified in the same class (e.g. in Class g - patient SAM041 - is also classified the patient in Class b - patient SAM032 - with a probability of the 70%). In order to verify the correlation between the grouping rules identified using the classification algorithm and the clustering algorithm, the EM clustering technique is performed. The EM algorithm is trained on V1-data and tested on V2-data in the same way.

```
 - Naive Bayes Classifier -
 Training on V1 & Test on V2

=== Confusion Matrix ===

  a  b  c  d  e  f  g   <-- classified as
 10  0  0  0  0  0  0 |  a = 28
  0  0  3  0  0  0  7 |  b = 32
  1  0  8  0  0  1  0 |  c = 33
  0  0  0  0  0 10  0 |  d = 34
  1  0  0  0  0  9  0 |  e = 38
  0  0  0  0  0 10  0 |  f = 39
  0  0  0  0  0  0 10 |  g = 41
```

FIGURE 4.11: Confusion Matrix of the Naive Bayes Classifier splitting TrainV1/TestV2 mode.

The Gaussian Mixture model based algorithm is tested setting the k value equal to 4, the maximum number of groups that may be identified in the confusion matrix in figure 4.11. In figure 4.12 the graph shows each patient (x-axis), with its clinical UPDRS_UP_kin_Exp score (y-axis), matched with the coloured cluster in which it is grouped.
Comparing the results obtained in figures 4.11 and 4.12 a strong correlation is identified between the classification and the clustering grouping rules. Indeed, the patients SAM032 and SAM041 result clustered in the same blue group (matching in class g), as well as the patient SAM028 in the green one (matching in class a) and the remaining part in the red cluster. The only mismatching results are related to the patient SAM033: it is grouped in the red cluster (matching in class f) in the EM algorithm, while it is

classified in the Class *f* with a probability of only 10% using the Bayesian classifier.

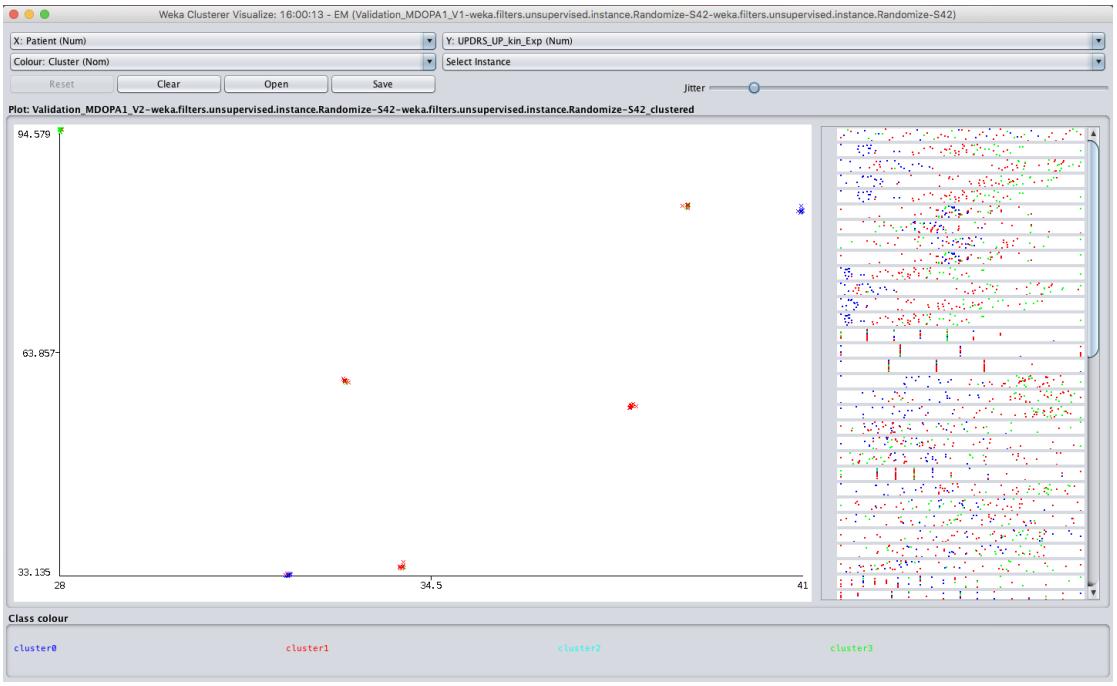

FIGURE 4.12: EM algorithm splitting TrainV1/TestV2 mode, k value equal to a number of 4 clusters.

Finally, in the figures 4.13 and 4.14 are shown, respectively, the results of the Naive Bayes classifier and the EM clustering algorithm applied both using the V2-data as training set and V1-data as test set. In that case, relating to the Gaussian mixture model based algorithm, the k value is not set a-priori. This because, in the confusion matrix in figure 4.13, some predictions may associate a patient within a class or in another with probabilities of 50%. So it has been considered to be inappropriate to choose a k value a-priori.

```
 - Naive Bayes Classifier -
 Training on V2 & Test on V1

=== Confusion Matrix ===

  a  b  c  d  e  f  g   <-- classified as
  2  0  8  0  0  0  0 |  a = 28
  0  0  0  0  0  0 10 |  b = 32
  0  0  0  0  0 10  0 |  c = 33
  0  0  5  0  0  5  0 |  d = 34
  1  0  0  0  0  9  0 |  e = 38
  0  0  0  0  0 10  0 |  f = 39
  0  0  0  0  0  0 10 |  g = 41
```

FIGURE 4.13: Confusion Matrix of the Naive Bayes Classifier splitting TrainV2/TestV1 mode.

The outcomes in figure 4.14 evidence the strong correlation between the Bayesian and the clustering grouping rules. The EM algorithm, trained on the V2 dataset, has identified 5 different clusters. As asserted in the previous analysis, the patients SAM032 and SAM041 result classified and clustered in the same blue group (matching in class g). The patient SAM028 is classified and also clustered in a separate class or cluster (green cluster matching in class c) as well. The remaining subjects, again, are classified and clustered in the same class or cluster (red cluster matching in class f).
Obviously, the results achieved using the clustering technique are related to the maximum log-likelihood value obtained among the different seed numbers tested.

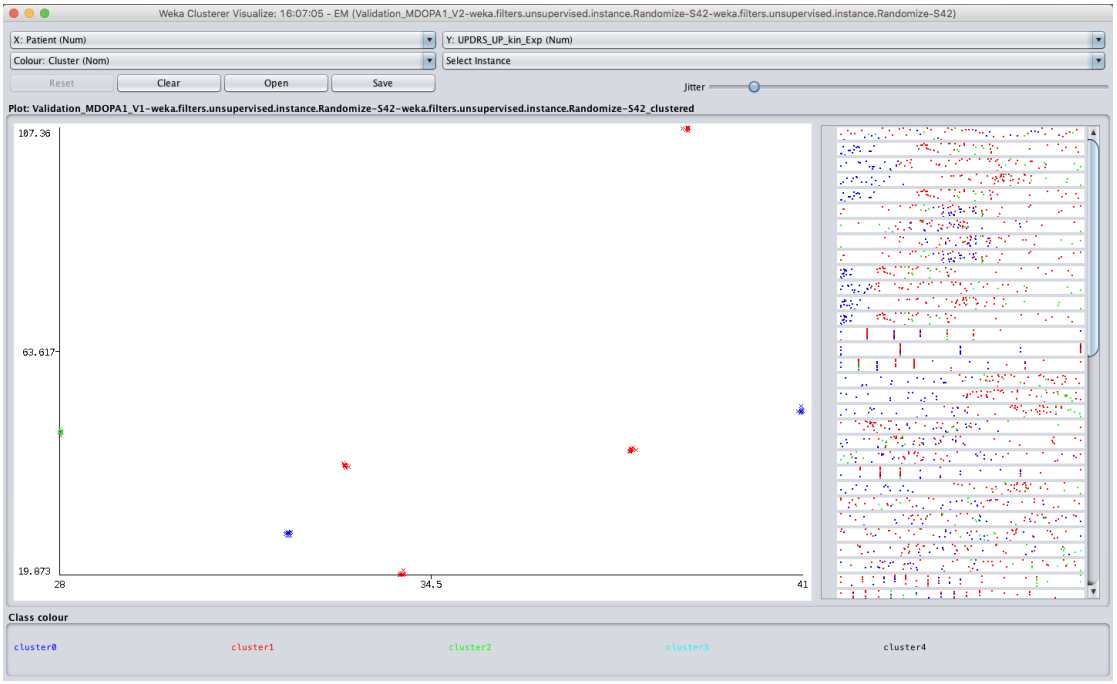

FIGURE 4.14: EM algorithm splitting TrainV2/TestV1 mode, k value equal to a number of undefined (-1) clusters.

Chapter 5

Conclusion and suggestions for future work

In this study has been proposed an instrument able to estimate the condition of the motor functions in patients with Parkinson disease. The estimates have been done basing on 3-axial accelerometer signals and features extracted to emulate the cardinal motor symptoms in PD. The defined features have proved to be relevant to, finally, predict the clinical status of different subjects.

EM clustering technique has been given preference over K-means, given the greater stability of the Gaussian mixture model based algorithm. As a result of the EM grouping tests, performed on the home-monitoring recordings, the instrument has proved to be able to detect the inter- variability of the motor functions of several patients.

The latter achievement has been validated through probabilistic classification assessments. The outcomes of the Naive Bayes classifiers, applied in *train/test* testing mode, have achieved a mean value of 83.13% of accuracy.

Furthermore, the EM clustering technique has been tested on the accelerometer signals of the tasks performed during V1 and V2 visits, since after each motor task clinical scores were available. The ultimate goal of this latter test was to identify a relationship between the estimates of the grouping algorithm and the clinical rating scores. The results show that there is a partial, but not total, correlation between the estimated clusters and the MDS-UPDRS-III assessments. This was mainly due to the lack of a consistent disease evaluation method; the MDS-UPDRS-III objective motor evaluations have been done by two different neurologists in V1 and V2 visits, also switching each other from one patient to the other. Surely, future validation procedures may be assessed comparing the estimates with a more accurate clinical target scale.

Nevertheless, grouping rules have been defined, since the same patient groups, identified using clustering techniques, have been predicted by the Naive Bayes classifiers as well. These latter results may be considered as the validation of what we obtained with the clustering algorithms. Therefore, it can be stated that the motor functions predictor is also able to group the patients on the basis of specific rules. Hence the need to understand if the identified rules are linked to any clinical status estimate of PD patients.

In the last analysis, it has been assumed that the MDS-UPDRS-III objective motor rating scale may be an evaluation procedure too generalized for our study. The creation of a new rating scale, based on the previous MDS-UPDRS-III scale, could be the next step to validate our motor functions predictor.
Once the grouping algorithm has been validated, it may be regarded as a suitable instrument to detect and to score the main characteristics of the abnormal movements in PD. The ultimate goal is to use the instrument in the sleep periods preceding the SB phenomenon. The aim is to analyze a primary relationship between sleep and motor functions in PD, and to understand the nature of this inconstant SB occurrence.
So, the next future outcome would be, firstly, to detect the change of objective measures of motor performance between morning (M-30) and evening (E) assessments, within the same subjects. The additional valuable outcome may be to recognize a change of objective measures of morning motor tasks at awakening from REM sleep, compared to the morning motor performance at awakening from NREM sleep, always within the same subjects.
Moreover, RBD and pseudo-RBD events are, definitely, considered to be other interesting testing periods. During these phenomena the complex motor behaviours are supposed to be more fluent and vigorous than the voluntary movements performed by the same patients during wakefulness. So the validated motor detector instrument, in a future application, may be used to characterize and to score these motor complex behaviours of the PD patients.

Appendix A

Python Codes

STEP 1

A.1 Data Extraction

```
# The code reported is related to the data extraction of M-DOPA+1 tests
# during 2 weeks recordings, visits V1 and V2;
# the same procedure is provided for the M-30, A-DOPA, E tests.
# The code is applied on data sampled at 40Hz (2 weeks recordings)
# and 100Hz (V1 and V2 visits).

# SAMXXX where XXX = 021 : 041
# FitTest File (e.g. SAM023_fittest.csv)
# Actigraph File 2weeksRec
# (e.g. SAM-023_right wrist_027366_2017-04-13 19-29-30.csv )
# Actigraph File V1
# (e.g. SAM-023_right wrist_V1_030570_2017-04-14 09-02-57.csv )
# Actigraph File V2
# (e.g. SAM-023__right wrist_V2_030570_2017-04-28 09-02-37.csv )

import pandas as pd
import datetime

data = pd.read_csv("SAMXXX_fittest.csv")
DataRuolo = data.set_index("RUOLO")
DataUser = DataRuolo.loc["USER",:]
DataHand = DataUser.set_index("HAND")
DataLeft = DataHand.loc["LEFT",:]
#RIGHT if the affected hand of the patient is right
DataKEY_PRESS_TIME = DataLeft.set_index("KEY_PRESS_TIME")
DataZero = DataKEY_PRESS_TIME.loc[0,:]
DataKEY_CODE =  DataZero.set_index("KEY_CODE")
DataStart = DataKEY_CODE.loc[29,:]
DataSESSION=DataStart.set_index("SESSION")
```

```
DataMDOPA1 = DataSESSION.loc['MDOPA1',:]
StartingTest = DataMDOPA1.iloc[:, 1:2]
StartingTest['DATE'] = pd.to_datetime(StartingTest.DATE)
one_hour = datetime.timedelta(minutes=60)
# if hh +2:00
StartingTest['DATE'] = StartingTest['DATE']+one_hour+one_hour
# if hh +1:00
# StartingTest['DATE']+one_hour

StartingTest.to_csv('MDOPA1StartPatient.csv')
# saving the extracted starting time of the FitTest in a .csv file

Fit = pd.read_csv('MDOPA1StartPatient.csv')
FitStart = Fit.iloc[:,1:2]
FitStart['DATE'] = pd.to_datetime(FitStart['DATE'])
# if data sampled at 40Hz
FitStart['DATE']= FitStart['DATE'].apply(lambda t: t.replace(microsecond=25000))
# if data sampled at 100Hz
# FitStart['DATE']= FitStart['DATE'].apply(lambda t: t.replace(microsecond=10000))
DataDATE=FitStart.set_index("DATE")
DataDATE.to_csv('MDOPA1_StartPatient.csv')
FitStart = pd.read_csv('MDOPA1_StartPatient.csv')
for i in FitStart['DATE']:
    i = i.replace('.',':')
    FITStart.append(i)
keys = set(line.strip() for line in FITStart)

# Function to extract 40seconds of the tests perfomed each day
# from the big data file (Actigraph recordings)
# case of 40 Hz recordings - (40seconds = 1600 samples)

def filter_lines(in_filename, out_filename, keys):
    with open(in_filename, 'r') as in_f, open(out_filename, 'w') as out_f:
        NUM=-1
        NUM_end=0
        for num,line in enumerate(in_f,1):
            date_end = line.find(',')
            if line[:date_end] in keys:
                NUM=num
                NUM_end=num+1599
                out_f.write(line)
            elif NUM<=num<=NUM_end:
                print(line)
                out_f.write(line)

filter_lines('SAM-XXX_right wrist_027366_2017-04-13 19-29-30.csv',
'SAMXXXMDOPA1.csv', keys)

DATA = pd.read_csv('SAMXXXMDOPA1.csv')
```

STEP 3

A.2 DataSet Construction

```
# The code reported is related to the dataset construction of M-DOPA+1 tests
# during 2 weeks recordings, visits V1 and V2;
# the same procedure is provided for the M-30, A-DOPA, E tests.
# The code is applied on data sampled at 40Hz (2 weeks recordings)
# and 100Hz (V1 and V2 visits).

# Note: 40 Hz 2 weeks recordings - labels of UPDRS info removed

# Example Code Visit V1

import pandas as pd
from pandas.io.excel import ExcelWriter

data = pd.read_csv("ValidationSet_MDOPA1_V1.csv", header=None)
data.columns = ['RMS_X','RMS_Y','RMS_Z','RMS_Seg','MEAN_X','MEAN_Y','MEAN_Z',
                'MEAN_Seg','VAR_X','VAR_Y','VAR_Z','VAR_Seg',
                'PEAKfreqs_X (0.5-10Hz) ','PEAKfreqs_Y (0.5-10Hz)',
                'PEAKfreqs_Z (0.5-10Hz)','PEAKfreqs_Power_X (0.5-10Hz)',
                'PEAKfreqs_Power_Y (0.5-10Hz)','PEAKfreqs_Power_Z (0.5-10Hz)',
                'MEANfreqs_X (0.5-10Hz)','MEANfreqs_Y (0.5-10Hz)',
                'MEANfreqs_Z (0.5-10Hz)','PEAKfreqs_Seg (0.5-10Hz)',
                'PEAKfreqs_Seg_Power (0.5-10Hz)','MEANfreqs_Seg (0.5-10Hz)',
                'PERIODICITY_X','PERIODICITY_Y','PERIODICITY_Z',
                'PERIODICITYSeg','PEAKfreqs_X (3.5-20Hz)',
                'PEAKfreqs_Y (3.5-20Hz)','PEAKfreqs_Z (3.5-20Hz)',
                'PEAKfreqs_Power_X (3.5-20Hz)','PEAKfreqs_Power_Y (3.5-20Hz)',
                'PEAKfreqs_Power_Z (3.5-20Hz)','MEANfreqs_X (3.5-20Hz)',
                'MEANfreqs_Y (3.5-20Hz)','MEANfreqs_Z (3.5-20Hz)',
                'PEAKfreqs3D (3.5-20Hz)','PEAKfreqs3D_Power (3.5-20Hz)',
                'MEANfreqs3D (3.5-20Hz)','PERCENTAGE_power_X',
                'PERCENTAGE_power_Y','PERCENTAGE_power_Z','PERCENTAGE_power3D',
                'Velocity_mean_X','Velocity_mean_y','Velocity_mean_z',
                'Velocity_mean_Seg','Velocity_Var_X','Velocity_Var_y',
                'Velocity_Var_z','Velocity_Var_Seg','LevoEquivalent',
                'Patient','UPDRS','UPDRS_UP','UPDRS_UP_kin',
                'UPDRS_UP_kin_Exp','UPDRS_UP_kin_Affected',
                'UPDRS_UP_kin_Affected_Exp'
                ]
data

Dataindex = data.set_index("RMS_X")
Dataindex.to_csv('Validation_MDOPA1_V1.csv')

with ExcelWriter('Validation_MDOPA1_V1.xlsx') as ew:

pd.read_csv("Validation_MDOPA1_V1.csv").to_excel(ew, sheet_name="Validation_MDOPA1_V1.csv")
```

```
# To obtain the data related to Visit V1/V2 of the all tests
# performed merged E, M-30 and M-DOPA+1 load as
# data = pd.read_csv("ValidationSet_V1.csv", header=None)
# where in "ValidationSet_V1.csv" file there are the data desired

# To obtain the data related to Visit V1 and V2 of the all tests
# performed merged E, M-30 and M-DOPA+1 load as and use the following commands
# v1 = pd.read_csv("Validation_V1.csv")
# v2 = pd.read_csv("Validation_V2.csv")
# frames = [v1,v2]
# v1v2 = pd.concat(frames)
```

Appendix B

MatLab Codes

STEP 2

B.1 Pre-Processing and Features Extraction

```
# The code reported is related to the dataset Pre-Processing and
# Features Extraction procedure of M-DOPA+1 tests
# during 2 weeks recording, visits V1 and V2;
# the same procedure is made for the M-30, A-DOPA, E tests.
# The code is used on data sampled at 40Hz (2 weeks recording)
# and 100Hz (V1 and V2 visits).


# SAMXXX where XXX = 021 : 041
# In SamXXXwsp.mat are saved the data extracted from the Python Code
# of 2 weeks recording, visits V1 and V2 for M30, M-DOPA+1, A-DOPA and E tests.

# Example Code 100 Hz recording

%%
close all
clear all
load('SamXXXwsp.mat') % change patient info

fs = 100; # or 40Hz
ts = 1/fs;
t40s = 0:ts:(40-ts);
t30s = 0:ts:(30-ts);
t20s = 0:ts:(20-ts);

DataMDOPA1 = SAMXXXMDOPA1V1(:,2:4);
DataMDOPA1 = cell2mat(DataMDOPA1);
DataMDOPA1 = DataMDOPA1*9.80665;
```

```
RowsMDOPA1 = length(DataMDOPA1);
Sample40s = length(t40s);
Sample30s = length(t30s);
Sample20s = length(t20s);

% INFO DAY NUMBER

DayMDOPA1 = SAMXXXMDOPA1V1(:,1);
counter=1;
for i = 0:Sample40s:(RowsMDOPA1-Sample40s)
K = DayMDOPA1(i+1);
NDayMDOPA1(counter) = K;
counter = counter+1;
end
NDayMDOPA1 = NDayMDOPA1';
```

B.1.1 Raw Data Features - Acceleration

```
%% High-Pass filter 0.5Hz and Low-Pass Filter 20Hz and 10Hz

% Design the digital Butterworth second order high and low pass filters :
% series of high pass and low pass filters cutoff frequency 0.5Hz and 10Hz,20Hz

Fhigh = 0.5;
Flow20 = 20;
Flow10 = 10;

[z,p] = butter(2,Fhigh/(fs/2),'high');
[d,c]= butter(2,Flow20/(fs/2));
[b,a]= butter(2,Flow10/(fs/2));

index_limit = 20-2;
SlidingInterval = 2;
StepInterval = 2;
NumberInterval = 10;

# The following code is reported for MDOPA1 test;
# same code valid for M30 and Evening

%% MDOPA1

% First for used to select 20-second interval from the accelerometer raw data

FEATUREINDEX = 0;

for INDICE = 0:Sample40s:(RowsMDOPA1-Sample40s)

    DataMDOPA1_20s = DataMDOPA1(INDICE+1001:INDICE+Sample40s-1000,:);
    SegAcc_20sec = sqrt(((DataMDOPA1_20s(:,1)).^2)+((DataMDOPA1_20s(:,2)).^2)+((
    DataMDOPA1_20s(:,3)).^2));
```

```
% Filter the data and the seg data (filtfilt - Zero Phase - automated
compensated delay)
RawFilteredF0_5Hz = filtfilt(z,p,DataMDOPA1_20s);
RawFilteredF20Hz = filtfilt(d,c,RawFilteredF0_5Hz);
RawFilteredF10Hz = filtfilt(b,a,RawFilteredF0_5Hz);

SegFilteredF0_5Hz = filtfilt(z,p,SegAcc_20sec);
SegFilteredF20Hz = filtfilt(d,c,RawFilteredF0_5Hz);
SegFilteredF10Hz = filtfilt(b,a,SegFilteredF0_5Hz);

% Second for used to select 2 seconds sliding step by step (NumberInterval
total events)

for indice = 0:StepInterval:index_limit

    Acc_2s = RawFilteredF20Hz((indice*fs)+1:(indice+SlidingInterval)*fs,:);
    LimAcc_2s = RawFilteredF10Hz((indice*fs)+1:(indice+SlidingInterval)*fs,:)
;

    SegAcc_2sec = SegFilteredF20Hz((indice*fs)+1:(indice+SlidingInterval)*fs
,:);
    LimSegAcc_2sec = SegFilteredF10Hz((indice*fs)+1:(indice+SlidingInterval)*
fs,:);

    % INTENSITY feature : Root Mean Square RMS

    Rms_AccXYZ_2s = rms(Acc_2s);
    Rms_SegAcc_2s = rms(SegAcc_2sec);

    % DYNAMIC features : MEAN and VARIANCE of acceleration raw data

    Mean_AccXYZ_2s = mean(Acc_2s);
    Mean_SegAcc_2s = mean(SegAcc_2sec);

    Var_AccXYZ_2s = var(Acc_2s);
    Var_SegAcc_2s = var(SegAcc_2sec);

    % RATE OF MOVEMENT : peak frequency
    %       AND
    % PERIODICITY : ratio of power associated with the dominant frequency
    % component to the total energy in the range 0.5-10Hz

    NFFT = length(Acc_2s);

    for K = 1:3

    % Power spectrum is computed when you pass a 'power' flag input
    [P,F] = periodogram(LimAcc_2s(:,K),[],NFFT,fs,'power');
    PdBW = 10*log10(P);

    % Find peak frequency - frequency with the larger power for each axis
    [peakPowers_dBW, peakFreqIdx] = max(PdBW);
    peakFreqs_Hz = F(peakFreqIdx);
    PeakFreqsPower_dBW(K) = peakPowers_dBW;
    PeakFreqs_Hz(K) = peakFreqs_Hz;
```

```
    % Control Peak frequency Outlier data using mean frequency scanning

    MeanFreqs_Hz(K) = meanfreq(P,F);

    % PERIODICITY : ratio of power associated with the dominant frequency
    % component to the total energy in the range 0.5-10Hz

    pband = bandpower(P,F,[peakFreqs_Hz-0.1 peakFreqs_Hz+0.1],'psd');
    ptot = bandpower(P,F,'psd');
    per_power = 100*(pband/ptot);
    PeriodicityXYZ(K) = per_power;

    end

    % Power spectrum is computed when you pass a 'power' flag input
    [Pseg,F] = periodogram(LimSegAcc_10sec,[],NFFT,fs,'power');
    PdBWseg = 10*log10(Pseg);

    % Find peak frequency - frequency with the larger power for each axis
    [peakPowers_dBWseg, peakFreqIdxseg] = max(PdBWseg);
    peakFreqs_Hzseg = F(peakFreqIdxseg);
    PeakFreqsPower_dBWseg = peakPowers_dBWseg;
    PeakFreqs_Hzseg = peakFreqs_Hzseg;

    % Control Peak frequency Outlier data using mean frequency
    % scanning

    MeanFreqs_Hzseg = meanfreq(Pseg,F);

    % PERIODICITY : ratio of power associated with the dominant frequency
    % component to the total energy in the range 0.5-10Hz
    pbandseg = bandpower(Pseg,F,[peakFreqs_Hzseg-0.1 peakFreqs_Hzseg+0.1],'
psd');
    ptotseg = bandpower(Pseg,F,'psd');
    per_powerseg = 100*(pbandseg/ptotseg);
    Periodicityseg = per_powerseg;

    % Store features values in a vector of NumberInterval values
    RMSfeature_MDOPA1((indice/StepInterval)+1,:) = Rms_AccXYZ_10s;
    RMSSegfeature_MDOPA1((indice/StepInterval)+1,:) = Rms_SegAcc_10s;
    MEANfeature_MDOPA1((indice/StepInterval)+1,:) = Mean_AccXYZ_10s;
    MEANSegfeature_MDOPA1((indice/StepInterval)+1,:) = Mean_SegAcc_10s;
    VARfeature_MDOPA1((indice/StepInterval)+1,:) = Var_AccXYZ_10s;
    VARSegfeature_MDOPA1((indice/StepInterval)+1,:) = Var_SegAcc_10s;
    PEAKfreqsfeature_MDOPA1((indice/StepInterval)+1,:) = PeakFreqs_Hz;
    PEAKfreqsPowerfeature_MDOPA1((indice/StepInterval)+1,:) =
PeakFreqsPower_dBW;
    MEANfreqsfeature_MDOPA1((indice/StepInterval)+1,:) = MeanFreqs_Hz;
    PEAKfreqsSegfeature_MDOPA1((indice/StepInterval)+1,:) = PeakFreqs_Hzseg;
    PEAKfreqsSegPowerfeature_MDOPA1((indice/StepInterval)+1,:) =
PeakFreqsPower_dBWseg;
    MEANfreqsSegfeature_MDOPA1((indice/StepInterval)+1,:) = MeanFreqs_Hzseg;
    PERIODICITYfeature_MDOPA1((indice/StepInterval)+1,:) = PeriodicityXYZ;
    PERIODICITYSegfeature_MDOPA1((indice/StepInterval)+1,:) = Periodicityseg;
```

```
    end

    % Store features values in a column vector to obtain TOT features

    RMSFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX*
    NumberInterval)+NumberInterval,:) = RMSfeature_MDOPA1;
    RMSSegFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX*
    NumberInterval)+NumberInterval,:) = RMSSegfeature_MDOPA1;
    MEANFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX*
    NumberInterval)+NumberInterval,:) = MEANfeature_MDOPA1;
    MEANSegFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX*
    NumberInterval)+NumberInterval,:) = MEANSegfeature_MDOPA1;
    VARFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX*
    NumberInterval)+NumberInterval,:) = VARfeature_MDOPA1;
    VARSegFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX*
    NumberInterval)+NumberInterval,:) = VARSegfeature_MDOPA1;
    PEAKfreqsFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX*
    NumberInterval)+NumberInterval,:) = PEAKfreqsfeature_MDOPA1;
    PEAKfreqsPowerFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX*
    NumberInterval)+NumberInterval,:) = PEAKfreqsPowerfeature_MDOPA1;
    MEANfreqsFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX*
    NumberInterval)+NumberInterval,:) = MEANfreqsfeature_MDOPA1;
    PEAKfreqsSegFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX*
    NumberInterval)+NumberInterval,:) = PEAKfreqsSegfeature_MDOPA1;
    PEAKfreqsSegPowerFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(
    FEATUREINDEX*NumberInterval)+NumberInterval,:) =
    PEAKfreqsSegPowerfeature_MDOPA1;
    MEANfreqsSegFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX*
    NumberInterval)+NumberInterval,:) = MEANfreqsSegfeature_MDOPA1;
    PERIODICITYFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX*
    NumberInterval)+NumberInterval,:) = PERIODICITYfeature_MDOPA1;
    PERIODICITYSegFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX*
    NumberInterval)+NumberInterval,:) = PERIODICITYSegfeature_MDOPA1;
    FEATUREINDEX = FEATUREINDEX+1;

end

%% Feature and corresponding day

for i=0:(RowsMDOPA1/Sample40s)-1

    RMSFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+NumberInterval,4)
    = (i+1);
    RMSSegFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+NumberInterval
    ,2) = (i+1);
    MEANFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+NumberInterval,4)
     = (i+1);
    MEANSegFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+NumberInterval
    ,2) = (i+1);
    VARFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+NumberInterval,4)
    = (i+1);
    VARSegFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+NumberInterval
    ,2) = (i+1);
```

```
    PEAKfreqsFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+
    NumberInterval,4) = (i+1);
    PEAKfreqsPowerFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+
    NumberInterval,4) = (i+1);
    MEANfreqsFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+
    NumberInterval,4) = (i+1);
    PEAKfreqsSegFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+
    NumberInterval,2) = (i+1);
    PEAKfreqsSegPowerFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+
    NumberInterval,2) = (i+1);
    MEANfreqsSegFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+
    NumberInterval,2) = (i+1);
    PERIODICITYFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+
    NumberInterval,4) = (i+1);
    PERIODICITYSegFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+
    NumberInterval,2) = (i+1);

end


%% Save variables

NameRawDataFeatures = ['RMS,','RMSSeg,','MEAN,','MEANSeg,','VAR,','VARSeg,','
    PEAKfreqs_1-10Hz,','PEAKfreqsPower_1-10Hz,','MEANfreqs_1-10Hz,','
    PEAKfreqsSeg_1-10Hz,','PEAKfreqsSeg_1-10Hz,','MEANfreqsSegPower_1-10Hz,', '
    MEANfreqsSeg', 'PERIODICITY', 'PERIODICITYSeg'];

RawDataFeatures_MDOPA1 = horzcat(RMSFEATURES_MDOPA1(:,1:3),RMSSegFEATURES_MDOPA1
    (:,1),MEANFEATURES_MDOPA1(:,1:3),MEANSegFEATURES_MDOPA1(:,1),
    VARFEATURES_MDOPA1(:,1:3),VARSegFEATURES_MDOPA1(:,1),PEAKfreqsFEATURES_MDOPA1
    (:,1:3),PEAKfreqsPowerFEATURES_MDOPA1(:,1:3),MEANfreqsFEATURES_MDOPA1(:,1:3),
    PEAKfreqsSegFEATURES_MDOPA1(:,1),PEAKfreqsSegPowerFEATURES_MDOPA1(:,1),
    MEANfreqsSegFEATURES_MDOPA1(:,1),PERIODICITYFEATURES_MDOPA1(:,1:3),
    PERIODICITYSegFEATURES_MDOPA1(:,1));


 # [...]  code M-30, A-DOPA, E


save('RawDataFeature_V1.mat','RawDataFeatures_M30','RawDataFeatures_MDOPA1','
    RawDataFeatures_Evening','NameRawDataFeatures')
```

B.1.2 Tremor Features

```
%% TREMOR PARAMETERS

% Frequency Analisys (frequency features)

%% High-Pass filter 3.5Hz and Low-Pass Filter 20Hz

% Design the digital Butterworth second order high and low pass filters :
% series of high pass and low pass filters cutoff frequency 1Hz,3.5Hz and 20Hz
```

```
Fpass = 1;
Fpass3_5 = 3.5;
Flow20 = 20;

% Design the digital Butterworth second order high pass filter cutoff frequency 1
    Hz
[z,p] = butter(2,Fpass/(fs/2),'high');
[z3_5,p3_5] = butter(2,Fpass3_5/(fs/2),'high');
[b,a]= butter(2,Flow20/(fs/2));

index_limit = 20-2;
SlidingInterval=2;
StepInterval = 2;
NumberInterval = 10;

# The following code is reported for MDOPA1 test;
# same code valid for M30 and Evening

%% MDOPA1

% First for used to select 20-second interval from the accelerometer raw data

FEATUREINDEX = 0;

for INDICE = 0:Sample40s:(RowsMDOPA1-Sample40s)

    DataMDOPA1_20s = DataMDOPA1(INDICE+1001:INDICE+Sample40s-2000,:);

    % Filter the data (filtfilt - Zero Phase - automated compensated delay)
    RawFilteredF1Hz = filtfilt(z,p,DataMDOPA1_20s);
    RawFilteredF20HzTOT = filtfilt(b,a,RawFilteredF1Hz);
    RawFilteredF3_5Hz = filtfilt(z3_5,p3_5,DataMDOPA1_20s);
    RawFilteredF20Hz = filtfilt(b,a,RawFilteredF3_5Hz);

    % Second for used to select 2 seconds sliding step by step (NumberInterval
    total events)

    for indice = 0:StepInterval:index_limit

        DataMDOPA1f1_2s = RawFilteredF20HzTOT((indice*fs)+1:(indice+
    SlidingInterval)*fs,:);
        DataMDOPA1f3_5_2s = RawFilteredF20Hz((indice*fs)+1:(indice+
    SlidingInterval)*fs,:);

        NFFT = length(DataMDOPA1f1_2s);

        for K = 1:3

            % Power spectrum is computed when you pass a 'power' flag input
            [P,F] = periodogram(DataMDOPA1f3_5_2s(:,K),[],NFFT,fs,'power');
            [Ptot,F] = periodogram(DataMDOPA1f1_2s(:,K),[],NFFT,fs,'power');

            PdBW = 10*log10(P);
```

```
        % Find peak frequency - frequency with the larger power for each axis
        [peakPowers_dBW, peakFreqIdx] = max(PdBW);
        peakFreqs_Hz = F(peakFreqIdx);
        PeakFreqsPower_dBW(K) = peakPowers_dBW;
        PeakFreqs_Hz(K) = peakFreqs_Hz;

        % Control Peak frequency Outlier data using mean frequency
        % scanning

        MeanFreqs_Hz(K) = meanfreq(P,F);

        % Percentage of the total power in the frequency interval between
        % peakF_Hz-0.1 peakF_Hz+0.1
        pband = bandpower(Ptot,F,[peakFreqs_Hz-0.1 peakFreqs_Hz+0.1],'psd');
        ptot = bandpower(Ptot,F,'psd');
        per_power = 100*(pband/ptot);
        PercentagePower(K) = per_power;

        P3(:,K) = P;
        Ptot3(:,K) = Ptot;

    end

    % Avaraged spectrum
    P3D = mean(P3');
    Ptot3D = mean(Ptot3');
    PdBW3D = 10*log10(P3D');

    % Find peak frequency - frequency with the larger power
    [peakPowers_dBW3D, peakFreqIdx3D] = max(PdBW3D);
    peakFreqs_Hz3D = F(peakFreqIdx3D);
    PeakFreqsPower_dBW3D = peakPowers_dBW3D;
    PeakFreqs_Hz3D = peakFreqs_Hz3D;

    % Control Peak frequency Outlier data using mean frequency
    % scanning

    MeanFreqs_Hz3D = meanfreq(P3D,F);

    % Percentage of the total power in the frequency interval between
    % peakF_Hz-0.1 peakF_Hz+0.1
    pband3D = bandpower(Ptot3D,F,[peakFreqs_Hz3D-0.1 peakFreqs_Hz3D+0.1],'psd
');
    ptot3D = bandpower(Ptot3D,F,'psd');
    per_power3D = 100*(pband3D/ptot3D);
    PercentagePower3D = per_power3D;

    % Store features values in a vector of NumberInterval values
    PEAKfreqsfeature_MDOPA1((indice/StepInterval)+1,:) = PeakFreqs_Hz;
    PEAKfreqsPowerfeature_MDOPA1((indice/StepInterval)+1,:) =
PeakFreqsPower_dBW;
    MEANfreqsfeature_MDOPA1((indice/StepInterval)+1,:) = MeanFreqs_Hz;
    PEAKfreqs3Dfeature_MDOPA1((indice/StepInterval)+1,:) = PeakFreqs_Hz3D;
    PEAKfreqs3DPowerfeature_MDOPA1((indice/StepInterval)+1,:) =
PeakFreqsPower_dBW3D;
```

```
        MEANfreqs3Dfeature_MDOPA1((indice/StepInterval)+1,:) = MeanFreqs_Hz3D;
        PERCENTAGEpowerfeature_MDOPA1((indice/StepInterval)+1,:) =
    PercentagePower;
        PERCENTAGEpower3Dfeature_MDOPA1((indice/StepInterval)+1,:) =
    PercentagePower3D;

    end

    % Store features values in a column vector to obtain TOT features
    PEAKfreqsFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX*
    NumberInterval)+NumberInterval,:) = PEAKfreqsfeature_MDOPA1;
    PEAKfreqsPowerFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX*
    NumberInterval)+NumberInterval,:) = PEAKfreqsPowerfeature_MDOPA1;
    MEANfreqsFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX*
    NumberInterval)+NumberInterval,:) = MEANfreqsfeature_MDOPA1;
    PEAKfreqs3DFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX*
    NumberInterval)+NumberInterval,:) = PEAKfreqs3Dfeature_MDOPA1;
    PEAKfreqs3DPowerFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX
    *NumberInterval)+NumberInterval,:) = PEAKfreqs3DPowerfeature_MDOPA1;
    MEANfreqs3DFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX*
    NumberInterval)+NumberInterval,:) = MEANfreqs3Dfeature_MDOPA1;
    PERCENTAGEpowerFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX*
    NumberInterval)+NumberInterval,:) = PERCENTAGEpowerfeature_MDOPA1;
    PERCENTAGEpower3DFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(
    FEATUREINDEX*NumberInterval)+NumberInterval,:) =
    PERCENTAGEpower3Dfeature_MDOPA1;
    FEATUREINDEX = FEATUREINDEX+1;

end

%% Tremor feature and corresponding day
for i=0:(RowsMDOPA1/Sample40s)-1

    PEAKfreqsFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+
    NumberInterval,4) = (i+1);
    PEAKfreqsPowerFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+
    NumberInterval,4) = (i+1);
    MEANfreqsFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+
    NumberInterval,4) = (i+1);
    PEAKfreqs3DFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+
    NumberInterval,2) = (i+1);
    PEAKfreqs3DPowerFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+
    NumberInterval,2) = (i+1);
    MEANfreqs3DFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+
    NumberInterval,2) = (i+1);
    PERCENTAGEpowerFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+
    NumberInterval,4) = (i+1);
    PERCENTAGEpower3DFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+
    NumberInterval,2) = (i+1);

end

%% Save variables
```

```
NameTremorFeatures = ['PEAKfreqs_3.5-20Hz,','PEAKfreqsPower_3.5-20H,','
    MEANfreqs_3.5-20H,','PEAKfreqs3D_3.5-20H,','PEAKfreqs3DPower_3.5-20H,','
    MEANfreqs3D_3.5-20H,','PERCENTAGEpower,','PERCENTAGEpower3D,'];

TremorFeatures_MDOPA1 = horzcat(PEAKfreqsFEATURES_MDOPA1(:,1:3),
    PEAKfreqsPowerFEATURES_MDOPA1(:,1:3),MEANfreqsFEATURES_MDOPA1(:,1:3),
    PEAKfreqs3DFEATURES_MDOPA1(:,1),PEAKfreqs3DPowerFEATURES_MDOPA1(:,1),
    MEANfreqs3DFEATURES_MDOPA1(:,1), PERCENTAGEpowerFEATURES_MDOPA1(:,1:3),
    PERCENTAGEpower3DFEATURES_MDOPA1(:,1));


 # [...]  code M-30, A-DOPA, E


save('TremorFeature_V1.mat','TremorFeatures_M30','TremorFeatures_MDOPA1','
    TremorFeatures_Evening','NameTremorFeatures')
```

B.1.3 Bradykinesia Features - Velocity

```
%% BRADYKINESIA PARAMETER
% (slowness)

% Velocity features
% VELOCITY : INTEGRATING ACCELEROMETER RAW DATA

%% High-Pass filter 0.5Hz and Low-Pass Filter 3.5Hz

% Design the digital Butterworth second order high and low pass filters :
% series of high pass and low pass filters cutoff frequency 0.5Hz and 3.5Hz

Flow = 3.5;
Fhigh = 0.5;

[z,p] = butter(2,Fhigh/(fs/2),'high');
[b,a]= butter(2,Flow/(fs/2));

index_limit = 20-2;
SlidingInterval=2;
StepInterval = 2;
NumberInterval = 10;

# The following code is reported for MDOPA1 test;
# same code valid for M30 and Evening

%% MDOPA1

% First for used to select 20-second interval from the accelerometer raw data

FEATUREINDEX = 0;

for INDICE = 0:Sample40s:(RowsMDOPA1-Sample40s)
```

```
DataMDOPA1_20s = DataMDOPA1(INDICE+1001:INDICE+Sample40s-1000,:);

% Filter the data and the seg data (filtfilt - Zero Phase - automated
compensated delay)
RawFilteredF0_5HzHz = filtfilt(z,p,DataMDOPA1_20s);
RawFilteredF3_5Hz = filtfilt(b,a,RawFilteredF1Hz);

% Integrator function (cumtrapz)

Velocity20sec = cumtrapz(t20s,RawFilteredF3_5Hz);

% Second for used to select 2 seconds sliding step by step (NumberInterval
total events)

for indice = 0:StepInterval:index_limit

        Velocity2sec = Velocity20sec((indice*fs)+1:(indice+SlidingInterval)*
fs,:);

        % Velocity 3D vector

        SegVelocity2sec = sqrt(((Velocity2sec(:,1)).^2)+((Velocity2sec(:,2))
.^2)+((Velocity2sec(:,3)).^2));

        % BRADY features : MEAN and VARIANCE of Velocity

        Mean_VelocityXYZ_2s = mean(Velocity2sec);
        MeanSegVelocity2sec = mean(SegVelocity2sec);

        Var_VelocityXYZ_2s = var(Velocity2sec);
        VarSegVelocity2sec = var(SegVelocity2sec);

        % Store features values in a vector of NumberInterval values (brady
        % features)
        BRADYmeanfeature_MDOPA1((indice/StepInterval)+1,:) =
Mean_VelocityXYZ_2s;
        BRADYmeanSegfeature_MDOPA1((indice/StepInterval)+1,:) =
MeanSegVelocity2sec;
        BRADYfeatureVar_MDOPA1((indice/StepInterval)+1,:) =
Var_VelocityXYZ_2s;
        BRADYfeatureVarSeg_MDOPA1((indice/StepInterval)+1,:) =
VarSegVelocity2sec;

end

    % Store features values in a column vector to obtain TOT brady features

    BRADYmeanFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX*
NumberInterval)+NumberInterval,:) = BRADYmeanfeature_MDOPA1;
    BRADYmeanSegFEATURES_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX
*NumberInterval)+NumberInterval,:) = BRADYmeanSegfeature_MDOPA1;
    BRADYFEATURESVar_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX*
NumberInterval)+NumberInterval,:) = BRADYfeatureVar_MDOPA1;
    BRADYFEATURESVarSeg_MDOPA1((FEATUREINDEX*NumberInterval)+1:(FEATUREINDEX*
NumberInterval)+NumberInterval,:) = BRADYfeatureVarSeg_MDOPA1;
```

```
        FEATUREINDEX = FEATUREINDEX+1;

end

%% Brady feature and corresponding day

for i=0:(RowsMDOPA1/Sample40s)-1
    BRADYmeanFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+
    NumberInterval,4) = (i+1);
    BRADYmeanSegFEATURES_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+
    NumberInterval,2) = (i+1);
    BRADYFEATURESVar_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+
    NumberInterval,4) = (i+1);
    BRADYFEATURESVarSeg_MDOPA1((i*NumberInterval)+1:(i*NumberInterval)+
    NumberInterval,2) = (i+1);
end

%% Save variables

NameBradyFeatures = ['BRADYmean,','BRADYmeanSeg,','BRADYVar,','BRADYVarSeg,'];

BradyFeatures_MDOPA1 = horzcat(BRADYmeanFEATURES_MDOPA1(:,1:3),
    BRADYmeanSegFEATURES_MDOPA1(:,1),BRADYFEATURESVar_MDOPA1(:,1:3),
    BRADYFEATURESVarSeg_MDOPA1(:,1));


 # [...]  code M-30, A-DOPA, E


save('BradyFeature_V1.mat','BradyFeatures_M30','BradyFeatures_MDOPA1','
    BradyFeatures_Evening','NameBradyFeatures')
```

Appendix C

List Of Figures

MDS-UPDRS-III (E)

---------- Normale ---------- Minimo ---------- Lieve ---------- Moderato ---------- Grave

	0	1	2	3	4	
3.1 Speech	○	○	◉	○	○	reset
3.2 Facial expression	○	◉	○	○	○	reset
3.3a Rigidity-neck	○	○	○	◉	○	reset
3.3b Rigidity-RUE	○	○	○	◉	○	reset
3.3c Rigidity-LUE	○	○	○	◉	○	reset
3.3d Rigidity-RLE	○	○	○	◉	○	reset
3.3e Rigidity-LLE	○	○	○	◉	○	reset
3.4a Finger tapping - Right hand	○	◉	○	○	○	reset
3.4b Finger tapping - Left hand	○	○	◉	○	○	reset
3.5a Hand movements - Right hand	◉	○	○	○	○	reset
3.5b Hand movements - Left hand	○	◉	○	○	○	reset
3.6a Pronation/supination - Right hand	○	◉	○	○	○	reset
3.6b Pronation/supination - Left hand	○	○	○	◉	○	reset
3.7a Toe tapping - Right foot	○	○	◉	○	○	reset
3.7b Toe tapping - Left foot	○	○	○	◉	○	reset
3.8a Leg agility - Right leg	◉	○	○	○	○	reset
3.8b Leg agility - Left leg	○	◉	○	○	○	reset

FIGURE C.1: MDS-UPDRS-III 33 item values in Evening Test V1 visit - Tremulous Patient SAM025.

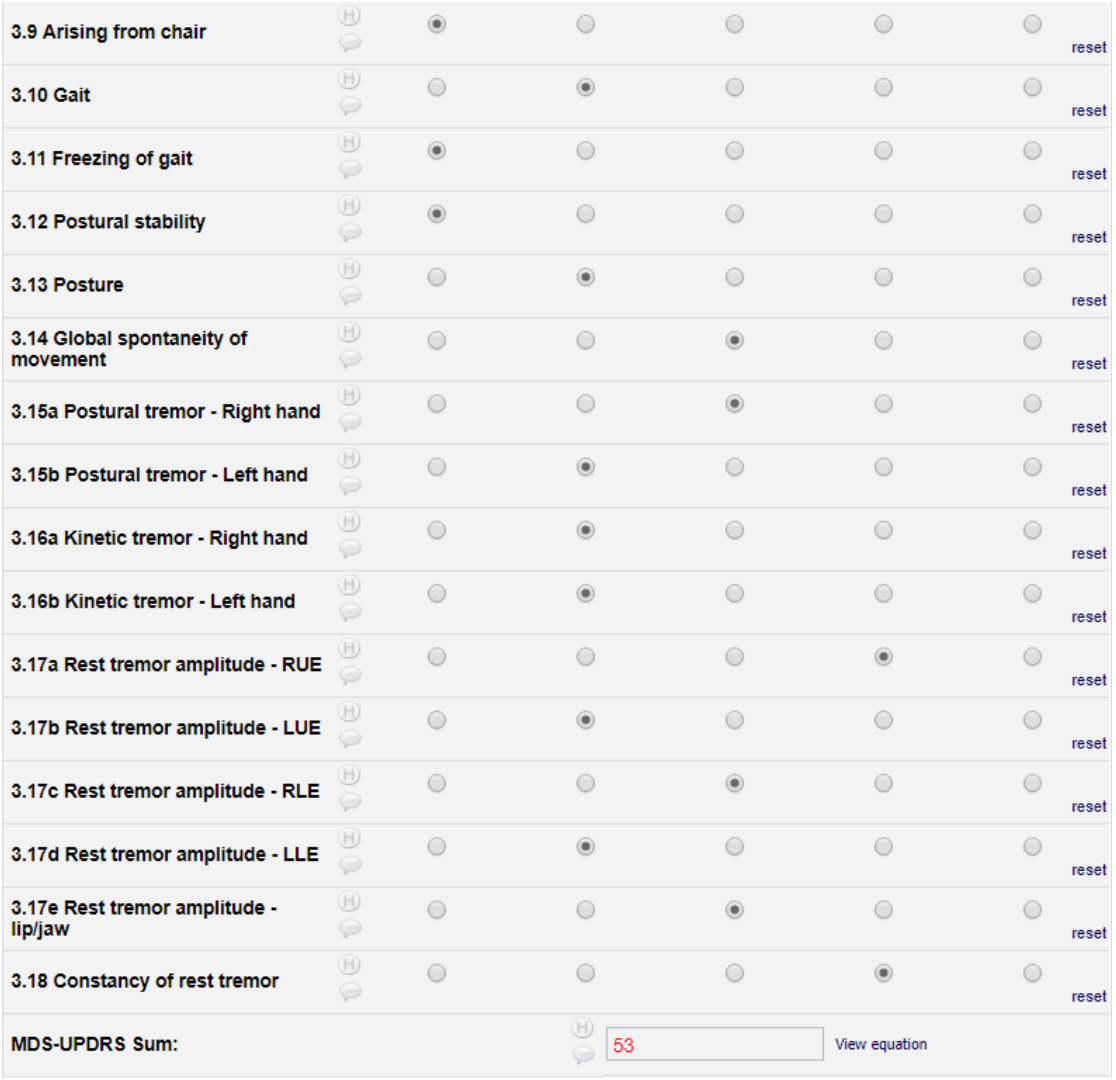

FIGURE C.2: MDS-UPDRS-III 33 item values in Evening Test V1 visit - Tremulous Patient SAM025.

Features_Fs (52)	DD 1	DD 2	DD 3	DD 4	DD 5	DD 6	DD 8	DD 9	DD 10	DD 11	DD 12	DD 13	Freq. Fs
RMS_X	1	1								1			3
RMS_Y	1	1	1	1	1		1				1		7
RMS_Z		1	1	1		1	1				1		6
RMS_Seg			1	1		1		1	1	1	1	1	8
MEAN_X													0
MEAN_Y													0
MEAN_Z													0
MEAN_Seg													0
VAR_X			1	1	1	1	1	1	1		1	1	9
VAR_Y						1		1	1	1		1	5
VAR_Z					1			1	1	1		1	5
VAR_Seg		1	1	1	1	1	1						6
PEAKfreqs_X (0.5-10Hz)	1	1	1	1	1	1	1	1	1	1	1	1	12
PEAKfreqs_Y (0.5-10Hz)	1	1	1	1	1	1	1	1	1	1	1	1	12
PEAKfreqs_Z (0.5-10Hz)	1	1	1	1	1	1	1	1	1	1	1	1	12
PEAKfreqs_Power_X (0.5-10Hz)	1	1	1	1	1	1	1	1	1	1	1	1	12
PEAKfreqs_Power_Y (0.5-10Hz)	1	1	1	1	1	1	1	1	1	1	1	1	12
PEAKfreqs_Power_Z (0.5-10Hz)	1	1	1	1	1	1	1	1	1	1	1	1	12
MEANfreqs_X (0.5-10Hz)	1	1	1	1	1	1	1	1	1	1	1	1	12
MEANfreqs_Y (0.5-10Hz)	1	1	1	1	1	1	1	1	1	1	1	1	12
MEANfreqs_Z (0.5-10Hz)	1	1	1	1	1	1	1	1	1	1	1	1	12
PEAKfreqs_Seg (0.5-10Hz)	1	1	1	1	1	1	1	1	1	1	1	1	12
PEAKfreqs_Seg_Power (0.5-10Hz)	1	1	1	1	1	1	1	1	1	1	1	1	12
MEANfreqs_Seg (0.5-10Hz)	1	1	1	1	1	1	1	1	1	1	1	1	12
PERIODICITY_X	1	1	1	1	1	1	1	1	1	1	1	1	12
PERIODICITY_Y	1	1	1	1	1	1	1	1	1	1	1	1	12
PERIODICITY_Z	1	1	1	1	1	1	1	1	1	1	1	1	12

FIGURE C.3: Feature frequency table resulting from the performance of CfsSubsetEval algorithm. "DD number of day" columns indicate the algorithm run deleting the "number of day" from the whole dataset during the training. "Freq. Fs (Fs - features)" column indicates the total number of time of occurrence of an attribute. In the last raw is reported the total number of selected features used in each different run.

PERIODICITYSeg	1	1	1	1	1	1	1	1	1	1	1	1	12
PEAKfreqs_X (3.5-20Hz)	1	1	1	1	1	1	1	1	1	1	1	1	12
PEAKfreqs_Y (3.5-20Hz)	1	1	1	1	1	1	1	1	1	1	1	1	12
PEAKfreqs_Z (3.5-20Hz)	1	1	1	1	1	1	1	1	1	1	1	1	12
PEAKfreqs_Power_X (3.5-20Hz)		1	1	1	1	1	1	1	1	1	1	1	11
PEAKfreqs_Power_Y (3.5-20Hz)	1	1	1	1	1	1	1	1	1	1	1	1	12
PEAKfreqs_Power_Z (3.5-20Hz)	1	1		1	1	1	1	1	1	1	1	1	11
MEANfreqs_X (3.5-20Hz)	1	1	1	1	1	1	1	1	1	1	1	1	12
MEANfreqs_Y (3.5-20Hz)	1	1	1	1	1	1	1	1	1	1	1	1	12
MEANfreqs_Z (3.5-20Hz)	1	1	1	1	1	1	1	1	1	1	1	1	12
PEAKfreqs3D (3.5-20Hz)			1										1
PEAKfreqs3D_Power (3.5-20Hz)	1												1
MEANfreqs3D (3.5-20Hz)	1	1		1	1	1	1	1	1	1	1	1	11
PERCENTAGE_power_X													0
PERCENTAGE_power_Y	1	1	1	1	1	1	1	1	1	1	1		11
PERCENTAGE_power_Z			1										1
PERCENTAGE_power3D	1	1	1	1	1	1	1	1	1	1	1	1	12
Velocity_mean_X	1	1	1	1	1	1	1	1	1	1	1	1	12
Velocity_mean_y			1					1				1	3
Velocity_mean_z	1	1		1	1	1	1	1	1	1		1	10
Velocity_mean_Seg											1		1
Velocity_Var_X	1	1	1	1	1	1	1	1	1	1	1	1	12
Velocity_Var_y	1	1	1	1	1	1	1	1	1	1	1	1	12
Velocity_Var_z	1	1	1	1	1	1	1	1	1	1	1	1	12
Velocity_Var_Seg	1	1	1	1	1	1	1		1	1			9
TOT Selected Features	36	38	39	39	38	39	38	38	38	38	37	37	

FIGURE C.4: Feature frequency table resulting from the performance of CfsSubsetEval algorithm. "DD number of day" columns indicate the algorithm run deleting the "number of day" from the whole dataset during the training. "Freq. Fs (Fs - features)" column indicates the total number of time of occurrence of an attribute. In the last raw is reported the total number of selected features used in each different run.

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